

The Terry Lectures

OURSELVES UNBORN

An Embryologist's Essay on Man

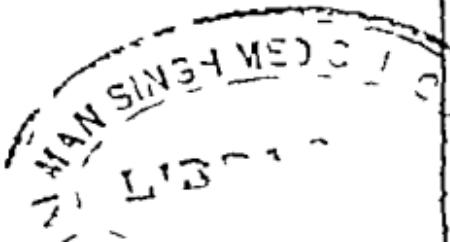
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OURSELVES UNBORN

*An
Embryologist's Essay
On Man*

BY
GEORGE W CORNER



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THE DWIGHT HARRINGTON TERRY FOUNDATION

LECTURES ON RELIGION IN THE LIGHT OF SCIENCE AND PHILOSOPHY

This volume is based upon the twenty-first series of lectures delivered at Yale University on the Foundation established by the late Dwight H. Terry of Bridgeport, Connecticut, through his gift of \$100,000 as an endowment fund for the delivery and subsequent publication of "Lectures on Religion in the Light of Science and Philosophy."

The deed of gift declares that "the object of this Foundation is not the promotion of scientific investigation and discovery but rather the assimilation and interpretation of that which has been or shall be hereafter discovered, and its application to human welfare, especially by the building of the truths of science and philosophy into the structure of a broadened and purified religion. The founder believes that such a religion will greatly stimulate intelligent effort for the improvement of human conditions and the advancement of the race in strength and excellence of character. To this end it is desired that lectures or a series of lectures be given by men eminent in their respective departments, on ethics, the history of civilization and religion, biblical research, all sciences and branches of knowledge which have an important bearing on the subject, all the great laws of nature, especially of evolution—also such interpretations of literature and sociology as are in accord with the spirit of this Foundation, to the end that the Christian spirit may be nurtured in the fullest light of the world's knowledge and that mankind may be helped to attain its highest possible welfare and happiness upon this earth."

"The lectures shall be subject to no philosophical or religious test and no one who is an earnest seeker after truth shall be excluded because his views seem radical or destructive of existing beliefs. The founder realizes that the liberalism of one generation is often conservatism in the next, and that many an apostle of true liberty has suffered martyrdom at the hands of the orthodox. He therefore lays special emphasis on complete freedom of utterance, and would welcome expressions of conviction from sincere thinkers of differing standpoints even when these may run counter to the generally accepted views of the day. The founder stipulates only that the managers of the fund shall be satisfied that the lecturers are well qualified for their work and are in harmony with the cardinal principles of the Foundation, which are loyalty to the truth, lead where it will, and devotion to human welfare.

To
The Distinguished Embryologists
Present and Former Colleagues
of the Author

GEORGE LINIUS STREETER

WARREN HARMON LEWIS

CARL G. HARTMAN

CHESTER HENRY HEUSER

ROBERT KYLE BURNS, JR.

PREFACE

THIS book represents the substance of the Terry Lectures given at Yale University in March, 1944. The intentions of the founder of the series, Mr Dwight Harrington Terry, are explained by the following words from his deed of gift:

"The object of this Foundation is the assimilation of that which has been or shall be hereafter discovered, and its application to human welfare, especially by the building of the truths of science and philosophy into the structure of a broadened and purified religion."

As a thoughtful friend of the author has remarked, the common ground upon which science and religion meet is found in the command "Seek, and ye shall find." The scientist may therefore properly accept the challenge of the Terry Lectureship by choosing from the discoveries and the current interpretations of his science those which he believes may help us understand our personal nature and our relation to the world about us. The science of the embryology of man has much to contribute—it touches closely upon the most intimate aspects of our nature, and in the past has been called upon for evidence in some of the great crises of theology and philosophy. One of the Early Fathers of the Church, Lactantius, became an embryologist, or at least a writer on the subject, to prepare himself for a pronouncement about the soul of the unborn infant. On the other hand, the thunders which Haeckel's embryological theories drew from 19th-century pulpits are not yet forgotten. We know not only from such passing controversies, but from the daily gropings of our thought on human problems, that those who seek to comprehend the spirit will always need to understand the body.

The author of this book, assuming no previous knowledge of biology on the part of his readers, aims to present a brief description of human development, its biological significance, and its aberrations, taking into account many recent discoveries, and emphasizing certain particular aspects which seem important for those who would construct their philosophy of life upon human realities.

Acknowledgements are due to several friends. The author's colleagues in the Department of Embryology of the Carnegie Institution, Dr G. L. Streeter, Dr C. H. Heuser, and Dr R. K. Burns, Jr., are well aware how much is owed to their instructive conversations at the laboratory lunch table this past winter Dr William L. Straus, Jr., of Johns Hopkins Medical School, expertly and helpfully criticized Chapter III. Dr Arthur T. Hertig of Harvard Medical School, Dr Philip Levine of the Newark (N. J.) Beth Israel Hospital, Dr Edwards A. Park, Professor of Pediatrics, Johns Hopkins University, Baltimore, Dr Frank B. Walsh of the Wilmer Ophthalmological Clinic, Johns Hopkins Hospital, and Dr Milislav Demerec of the Department of Genetics of the Carnegie Institution, at Cold Spring Harbor, Long Island, were good enough to read critically passages relating to subjects on which they are especially well informed. The Princeton University Press has kindly allowed the use in Chapter I of a passage from the author's previous book, *The Hormones in Human Reproduction* (1942). Photographs from the Carnegie Collection are by Chester F. Reather unless otherwise noted.

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THE EMBRYO AS GERM AND AS ARCHIVE

My substance was not hid from thee, when I was made in secret, and curiously wrought in the lowest parts of the earth. Thine eyes did see my substance, and in thy book all my members were written when as yet there was none of them.

1

WHEN a man is born, he is already nine months old. "Surely," says Sir Thomas Browne in *Religio Medici*, "we are all out of the computation of our age, and every man is some months older than he be-thinks him for we live, move, and have our being in that other World the womb of our Mother" The Chinese have long recognized this fact. Each of their babies is given at birth a full year's credit on the reckoning of its age. They know, of course, that the span of our prefatory existence is actually only nine months long, but fractions are a bother, and in China every man claims one more year of age than does a European born on the same day of the same year.

To the embryologist such a calculation seems eminently proper, for the months before birth are in their way the most eventful part of life and we spend them at a rapid pace. At its beginning the body consists of one cell by the time of birth it has two hundred billion cells. When you, gentle reader, were a single cell, you weighed about fifteen ten millionths of a gram at birth (if you were a seven pound baby) you weighed 3,250 grams. In those nine months you gained two billion times. You began as a spheri-

cal egg that could have been lost in a pinhole, you soon became hollow and then long and narrow. Some time in the third week of life (Chinese reckoning) your heart began to beat, was not that a great day in your career? You had the beginnings of a brain before you had hands, and of arms before legs, you developed muscles and nerves and began your struggle, in the darkness you faced strange perils, and you came at last to the threshold of the world.

And now, since you are comfortably reading this book, we know that your own first nine months were healthy and uneventful but if something had gone wrong, if your incipient life had flickered or failed, you might have become the object of great attentions. Had you reached a certain stage, the State would have intervened, saying that this creature was a living individual and therefore certificates must be filed with the registrar of vital statistics albeit the States are not very sure just when an embryo becomes a person a New Yorker, for example, must be certified earlier than a Marylander. The Church also might have spoken, saying that this infant, being so many days along, possessed an immortal soul and must be baptized before its last heartbeat, or else , although, to be sure, theologians of the various 'doxies do not agree as to the moment when the embryo achieves a soul.

Finally, had an embryologist been at hand, he would have claimed for science that speck of broken life, carefully studying it beneath his microscope, knowing that humanity is older than rites and records, and that even in the isolation of its dark chamber the human embryo is bound by ties of kinship to all life that ever lived upon earth, and yet is signed with peculiar traits that mark it a man-to-be. Its structure and its vital processes, if only they can be deciphered, will tell us much about the nature of our perplexing race and something perhaps of human fate and foreordination.

The development of the human being during the first week is unknown. No one has yet seen the embryo during its journey from the ovary through the Fallopian tube, until the time when it becomes implanted in the uterus. Only by deduction from other animals can we fill this gap and imagine, no doubt imperfectly, what the earliest stages must be.

Before it begins to develop, the precursor of the human embryo is a single cell, one of thousands which lie in the substance of the ovary awaiting possible release. The unfertilized and undeveloped human egg cell or *ovum* is of course well enough known, for all that is necessary to see it is to put a thin section of a suitable human ovary under the microscope, and to scan the inner wall of one of the numerous ovarian follicles for the one large cell that projects into the cavity. In every four weekly cycle of the mature woman one such follicle enlarges and ruptures. The ovum is discharged into the oviduct (Fallopian tube) and begins its journey toward the uterus. In recent years several persistent investigators, seizing opportunities afforded by surgical operations, have been able to recover and photograph human ova from the tubes. The pictures, made under great difficulties, are not very instructive for the present purpose, and our pen sketch (Fig. 1, C, D), together with the photograph of the mouse egg (Plate I, A) will serve to show the nature of this all important cell. Fig. 1 shows also the route of its journey to the uterus.

Although the ovum is the largest cell in the human body, it is a small thing by ordinary standards of comparison. It is about $\frac{1}{15}$ inch (140 mm.) in diameter, which means that if placed in a clear dish of water, in a good light, it can just barely be seen with the unaided eye. Under the microscope it is a tiny globule of protoplasm containing micro-

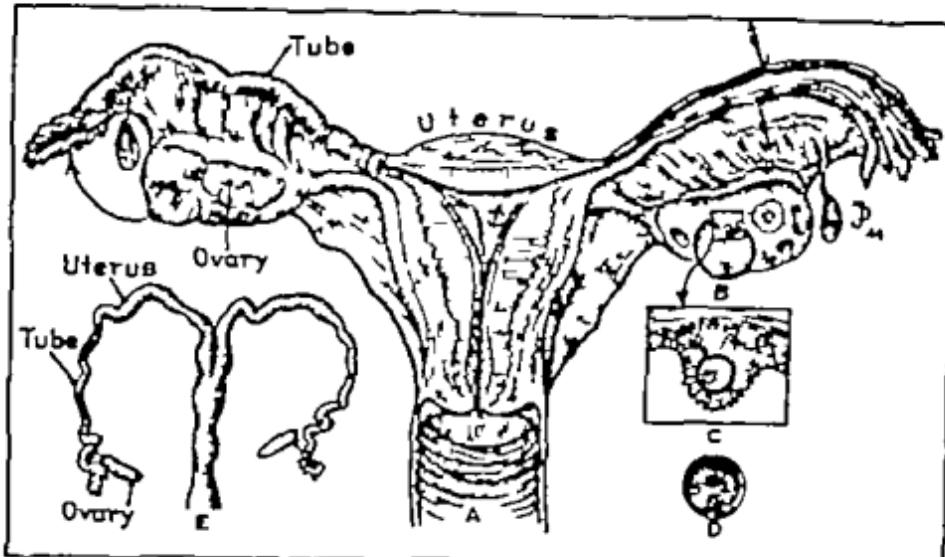


FIG. 1. A, diagram of human ovaries, oviducts (Fallopian tubes) and uterus, as seen from the rear. The right tube and the uterus are drawn as if opened by removal of their rear walls, to show the canal of the tube and the cavity of the uterus. The arrows at the left indicate the course of the ovum from ovary through tube to uterus. The dotted square indicates site of the early embryo shown in Plate III A-C, and in Fig. 8. Approximately one-half size. B, a ripe follicle in the ovary with egg cell (not to scale) in its wall. C, enlarged view of the egg hillock of the follicle in section. D, egg cell (ovum) external aspect, magnified about 30 diameters. E, two-horned uterus of rabbit, with oviducts and ovaries, approximately one-fourth natural size.

scopic fat droplets (yolk) and surrounded by a beautifully clear and regularly formed envelope of transparent substance. Cut into minutely thin sections and examined with the finest lenses, the ovum proves to contain the usual constituents of animal cells, including of course a nucleus with the chromosomes upon which its role in heredity depends but these details of internal cell structure must chiefly be studied in the more easily obtainable eggs of other animals, and do not concern us here.

If the ovum is unfertilized, it goes to pieces in the uterus after a few days and its remains, which are less than a grain of dust, disperse unnoticed. If however there has been a

mating, the sperm cells from the male meet the ovum in the oviduct and there one of them enters it. The substance of the two cells fuses, and in a few hours the ovum begins to divide.

The division of the unfertilized egg has long since been observed in various lower animals, especially in the aquatic forms such as the starfishes, marine worms, fishes, and amphibians. Their eggs are deposited in the water and it is easy enough to bring them under the microscope, in sea water or pond water as the case may be, so that their environment is not changed and the process of division goes on beneath the eyes of the observer. In mammals the case is different. The ova remain within the mother's body. Merely to find them demands considerable knowledge of the breeding habits and the reproductive cycles of the animals, knowledge which has had to be slowly acquired before the embryologist could begin his observation. The eggs when found are smaller than those of most lower animals and much more delicate. Being cells of warm-blooded animals, adapted to live only in the complex chemical environment of the mammalian body, they cannot survive in the outside world (except briefly in the hands of a modern tissue-culture expert, as will be mentioned in a moment). All that we have known, until very recently, about the early development of mammalian eggs has been gained by the expensive and tedious process of killing or operating upon a series of animals at regular intervals after mating. In this way the general features of the process have been traced in many species among the best known are the mouse, rat, rabbit, guinea pig, domestic pig, and rhesus monkey. Beginning in 1929 Dr Warren H. Lewis of the Carnegie Embryological Laboratory in Baltimore, aided by various coworkers, accomplished the feat of transferring the eggs of certain mammals to dishes of nutrient solution in a chamber regulated to body temperature, under the microscope. He was thus

able to watch and photograph for hours at a time the earliest stages of their development. The task is a difficult one, the artificial environment cannot exactly duplicate the favorable conditions existing in the mother's Fallopian tube and uterus, and therefore no ovum has ever been kept alive through more than a few cell divisions. By studying a sequence of rabbit eggs, however, removed from the mothers at successively later periods, Lewis and Gregory saw the whole living process from the stage of one cell to that of about four days, containing many scores of cells. Their motion pictures of these events have stirred a great many scientific audiences. Species other than rabbits seem to be less hardy. Much of the sequence has been followed, however, in the guinea pig. In the mouse and in the rhesus monkey (whose living eggs are of course much more troublesome and expensive to obtain than those of the domestic and laboratory animals) only the earliest divisions have been filmed, but at least the painstaking methods and the well-adjusted nutrient fluid have kept the eggs alive long enough for the making of superbly instructive still pictures.

I have chosen, to illustrate our present discussion, a series of photographs of the mouse egg by Lewis and Wright (Plate I). In the mouse, as in most mammals, the follicles ripen and discharge the eggs at regular intervals. The females are "in heat," as the breeders say, and accept the male at about the time when the follicles are mature. Two hours after mating the sperm cells are in the oviduct and one of them enters the egg. About 30 hours after mating the fer-

DESCRIPTION OF PLATE I

Segmentation of the fertilized egg of the mouse. A, one-cell stage; B two-cell stage, 31 hours after mating; C, four cells, 44 hours; D morula stage, 72 hours; E, early blastocyst, 82 hours; F blastocyst, 5 days after mating. Magnified 400 diameters. From *Contributions to Embryology*, Carnegie Institution of Washington, by courtesy of Warren H. Lewis and Elsie S. Wright.

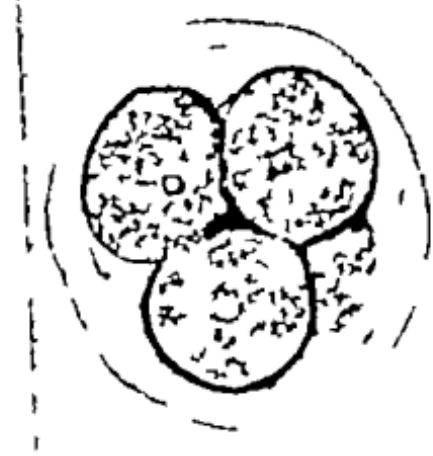
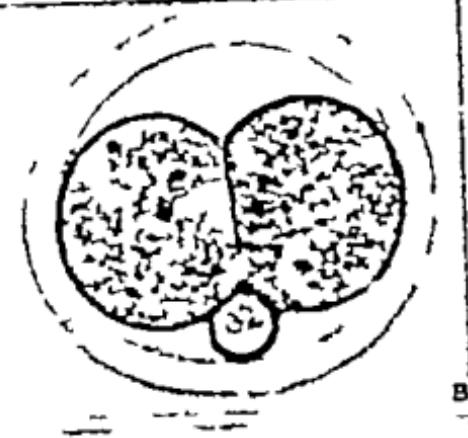
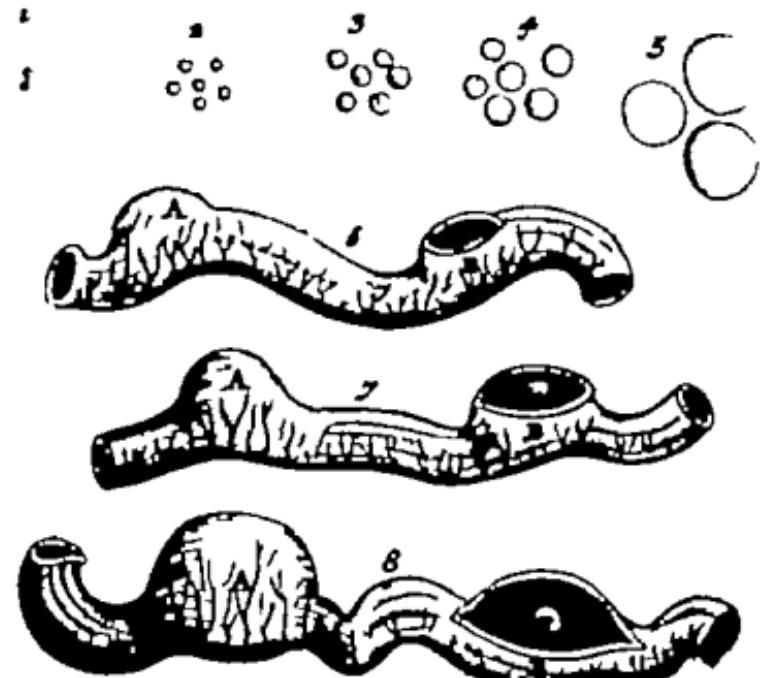
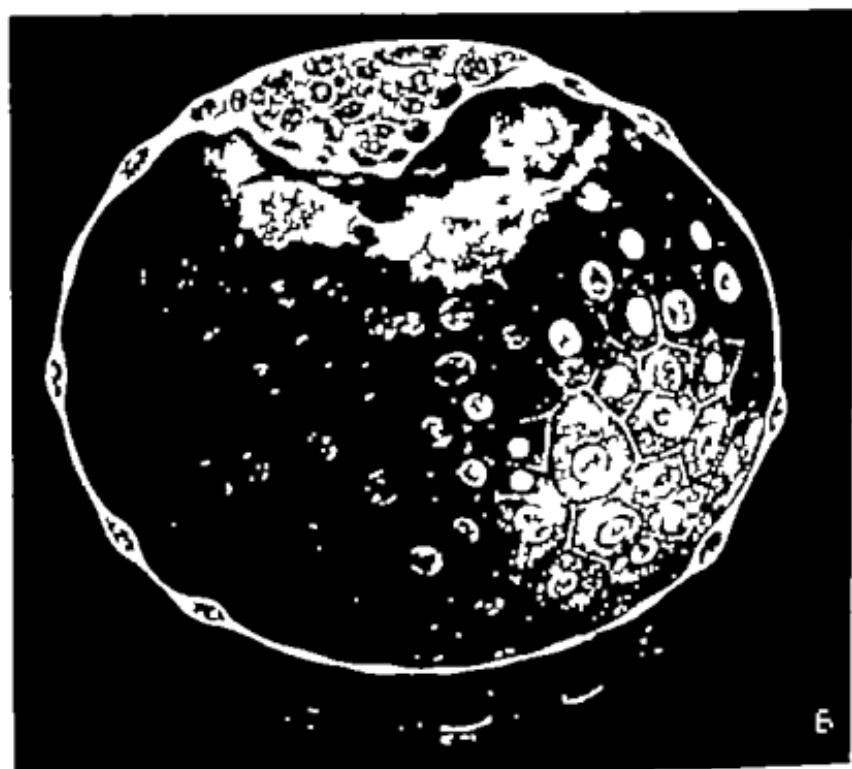


PLATE I



A



B

tilized egg divides (Plate I, B) At 45 hours there are 4 cells at 49 hours there are 8 At 72 hours the embryo is a rounded mass of cells (D), called by the Latin word *morula* because of its resemblance to a mulberry At this time the egg reaches the end of the tube and enters the uterus An embryo in this state was placed in tissue culture and observed for 4 hours during this time it developed an eccentrically placed cavity, as seen in Plate I, E. On the 5th and 6th days the embryo is a hollow sphere walled by a single layer of thin cells bearing at one pole an *inner cell mass* or aggregation of cells (F) An embryo like this is said to be a *blastocyst* using the Greek roots to signify a germinal sac.

No illustration could make the structure of a typical blastocyst more clear than James Didusch's drawing of a monkey embryo of the 9th day (Plate II, B)¹ The young animal has already acquired an easily visible degree of organization, for the outer layer of cells is going to furnish the membranes which surround the embryo proper and attach it to the mother, whereas the thickened inner cell mass will give rise to the embryonic body

The human embryo at 5 or 6 days must be a blastocyst of the same general type as those of the mouse and monkey but we do not know it by direct observation, for comparable

1. Made at the instance of Dr George L. Streeter by whose courtesy it is reproduced.

DESCRIPTION OF PLATE II

A, part of illustration (Tabula XXVI) in Regner de Graaf's *De organis generationis inversionibus* 1672, showing rabbit embryos from day 8 after mating (at 1 upper left) to day 10 (at 8) The blastocysts in the groups numbered 1 to 8 have been removed from oviduct or uterus; figures 6 to 8 show parts of uterine horns with the implantation sites Approximately natural size.

B blastocyst of monkey (Carnegie C.822) 9 days after mating, drawn by James F. Didusch. Magnified 300 diameters. From *Cooperation in Research* Carnegie Institution of Washington, 1938, by courtesy of G. L. Streeter

early human embryos are yet to be found. We do know that somewhat later stages which we possess in relative abundance are just as typically mammalian as those of other species. I have been careful, however, in referring to the unknown blastocyst, to say "the same general type," for there is also reason to suppose that the human embryo will even as a 5- or 6-day blastocyst show peculiarities of its own.

Biologists swing to extremes like other philosophers. To establish an idea it is often overstated. For a century past it has been the fashion among biologists to emphasize the interresemblance of all the vertebrate animals in their embryonic stages. They are of course profoundly similar in plan and aspect, and if we limit ourselves to the mammals, the resemblance is overwhelming. All of them pass through a blastocyst stage essentially like that of the mouse and monkey which we have illustrated. Before that, they all come from single-celled ova, which differ, as far as can be seen through the microscope, only in small details, about as much perhaps as two watches of different makes differ from each other. This resemblance is one of the strong arguments for the evolutionary doctrine that all the vertebrates are related to each other through a common ancestor.

In the days when the evolutionary hypothesis had to be fought for, the resemblance of embryos was insistently taught, until it gave rise to all sorts of exaggerated notions for example, that all vertebrate embryos are literally identical, or that human embryos have actual gills, like fish. This however is anticipating a subject that will be discussed later. The present point is that amid all the resemblances there are differences which go all the way back to the egg. Alike as the ova of the various mammals are, an expert can yet distinguish under the microscope, by small dissimilarities, the eggs of all these species which have as yet been fully described. I hope this will not give too much comfort to

those who do not relish the idea of man's relationship to the other animals.

When the ova grow into blastocysts, the differences increase. The blastocysts of certain animals are in fact very peculiar. The first investigator who ever made a systematic attempt to see early mammalian embryos—William Harvey, the genius who proved the circulation of the blood—made a great failure and involved the embryological ideas of his time in serious confusion, because without knowing it he had chosen to study an animal which has a very atypical blastocyst stage. The story is worth telling here not only because it will help in developing our theme but also because it is one of the most picturesque episodes in the history of science. Not every mistake has the honor to be made by the greatest scientist of his day, nor to be perpetrated in a royal palace and demonstrated to a king!

William Harvey had prepared himself for the attempt to discover early embryos of the higher animals by thorough study of the development of the hen's egg along lines laid down by his great teacher Fabricius in Italy. We have a glimpse of him through the eyes of a young student at Oxford in 1642, who saw Harvey and his friend George Bathurst working on chick embryos in the latter's rooms in Trinity College, where they kept a hen to incubate the eggs. When Harvey applied his studies to the mammals, he took advantage of his position as court physician to Charles I to dissect the fallow deer which the King and his companions assiduously hunted. As Harvey informs us, "the hind and the doe admit the male at one and one only particular season of the year, namely in the middle of September, after the Feast of the Holy Cross and they bring forth after the middle of June, about the Feast of St. John the Baptist." Beginning, then, in late September, the eager doctor began to dissect the female quarry of the King's hunt, looking into their uteri for some sign of an embryo like that of

the fowl. This search was futile. Neither in September, nor October, nor at any time until the middle of November was anything found that could be taken as an indication of pregnancy. As a crucial experiment the King ordered a dozen does to be taken alive just after the mating season and put into a paddock at Hampton Court Palace. These were killed at intervals as directed by Harvey, and finally in a preparation made about November 12 his keen eyes observed "mucous filaments like spiders' webs drawn through the uterus. These filaments becoming conjoined present themselves as a membranous and gelatinous tunic." In animals observed about November 18 to 21, in various years, a tiny object resembling the early chick embryo was visible in the middle of the filamentous strands. From this time on there was no further mystery—the embryos of does killed at later and later intervals were found to have grown as might be expected, and with surprising rapidity. In the course of 8 or 9 days more, says Harvey, "a foetus so perfect in all parts is seen that a male can be distinguished from a female, and the feet are formed, the hooves being cleft, the whole being of a mucous consistency and a pale yellowish color."

But what of the 7 blank weeks between mating and the first appearance of a recognizable embryo? It must be remembered that the great physiologist was working absolutely without benefit of previous information about mammalian embryos. What he could see with his own eyes was all the clue he had. He thought that he had been watching the development of an egg, and its transformation into an embryo, in the uterus from the beginning. The "filamentous tunic" he had seen more or less resembled the white-of-egg of the hen's egg, and the embryo appeared to develop in its midst after the fashion of a chick embryo. His mistake depended upon special peculiarities of reproduction in the deer, and was not fully explained for almost 300 years. For

lack of a microscope, Harvey was also involved in hopeless further uncertainty about the nature of fertilization and the role of the male parent in fecundation and inheritance.

The embryo, he thought, was secreted by the uterus in some such way as an idea is secreted by the brain. This concept, had it long survived, would have given us a strangely erroneous basis for our philosophy of human relationship no physical continuity of life the child a congealed exhalation of a secretory organ heredity conveyed by an idea the father a mere transient impulse at the start, contributing nothing to the substance of his offspring.

The next investigator who took up the difficult search, the young Dutchman Regner de Graaf (1641-73), luckily chose the rabbit for his experiments. His brilliant success is shown in our Plate II, A, part of the 26th plate of de Graaf's book of 1672. Proceeding upward from the bottom picture we see successively earlier stages of pregnancy. The embryos develop in little chambers, along each horn of the rabbit's two-pronged uterus. No. 8 shows the embryo of 10 days. On the 9th day (No. 7) the picture shows only a cloudy spot and on the 8th day nothing at all (No. 6), but de Graaf's text makes it clear that the uterine chambers contained what we should now call blastocysts attached lightly to the lining, and so delicate that they broke like bubbles when the uterus was opened. De Graaf was now seeing younger embryos than anyone had ever previously discovered. Going back successively to the 7th, 6th, 5th, and 4th days the little round cysts were found free in the uterus, and on the 3d day after mating (de Graaf's earliest successful observation) the small objects shown at No. 1 in his plate were discovered in the oviduct. Enchanted with this sight, the young physician made the correct assumption that the "eggs" could not have been secreted by the uterus but must have come from the organs formerly called the female testes, to which he now applied the term *ovary*.

Not until 1827 did the Estonian Karl Ernst von Baer complete the story by discovering (in the dog) the microscopic egg cell in the ovarian follicle and tracing it to the oviduct and thence to the uterus.

To return now to William Harvey's baffling experience with the deer, an explanation was found in 1854 when Theodor L. W. Bischoff of Hannover, armed with the experience of two centuries, again explored the early embryology of the deer. He discovered, first, the extraordinary fact that in this family of animals the blastocysts, once they reach the uterus, remain dormant for many weeks. The eggs are fertilized, as in other mammals, soon after they are discharged from the ovary. They segment as quickly as those of the rabbit, but once blastocysts are formed the processes of growth are delayed. In the European species (*Cervus capriolus*) which Bischoff examined, the waiting period is even longer than in the English fallow deer. During the weeks from late September until November, when Harvey found nothing, there actually were blastocysts in the uterus, of about the same size as those of the rabbit which de Graaf so clearly observed. But in the deer there are only two embryos in a litter, transparent wisps no bigger than a pin head, hidden in the extensive two-horned chamber of the uterus. No wonder Harvey never found them—not even he, whose great intellect had been the first to perceive the meaning of the heart's motion.

It will be remembered that when Harvey did find something in the uterus, about 7 weeks after mating, he described it as a gelatinous web of filaments. The explanation of this lies in a second peculiarity of the blastocysts of the deer family: when the period of dormancy is over, the rounded sacs suddenly grow lengthwise until they become limp, sticky tubular strings several inches long. The inner cell mass is still a mere dot at the mid point of the cyst. All these discoveries of Bischoff were confirmed in 1899–1906.

by Franz Keibel of Freiburg and his Japanese student Sakurai, from whose article I have taken a sketch of the elongating blastocyst (Fig. 2). The modern embryologist is able to remove such delicate structures intact by floating them out of the uterus, painstakingly opened under salt solution with fine scissors. Awkwardly caught up, however, on the knife-point of a 17th-century pioneer, they would stick and pull into formless tangles.

"Thus Harvey sought the truth in Truth's own book—*Creation*—which by God himself was writ,"

but found the writing dim, or vision blurred

The difference between the blastocysts of the deer and the rabbit, so vividly illustrated by the story of Harvey's and de Graaf's investigations, is merely one example of a general diversity among the early embryos of the various mammals. No two species are exactly alike in appearance.

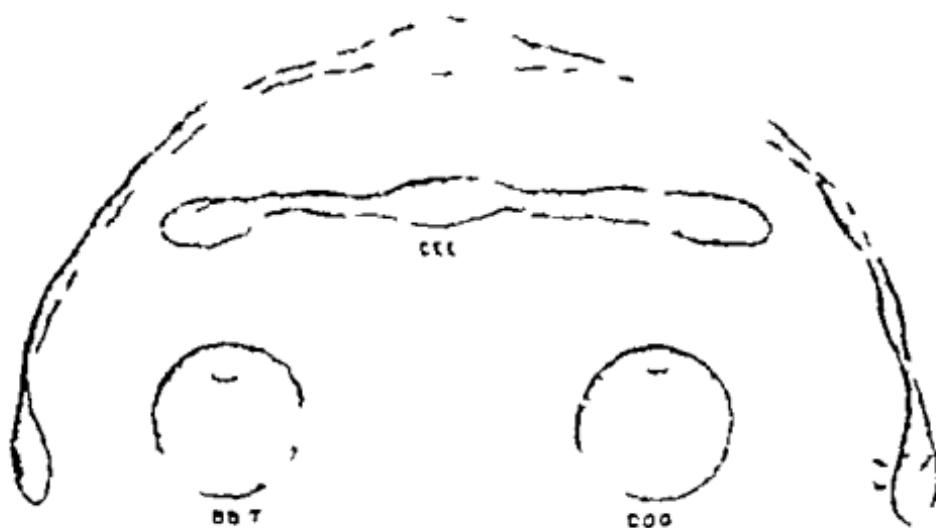


FIG. 2. Embryos of several species in the blastocyst stage showing the general forms which they attain before attachment. (Pig after Heuser; deer after Sakurai.) Note the small embryonic disc (inner cell mass) on each blastocyst. All magnified several diameters but not to exactly the same scale.

and rate of development. The hooved animals (ungulates) have elongated blastocysts like those of the deer. The sow's ovum for example has reached only the 4-cell stage when it arrives at the uterus, but in less than two weeks it grows to the enormous length of 30 centimeters, or more than one foot. A whole litter of such embryos, averaging ten individuals, and sometimes numbering two dozen, can only be accommodated in the uterus because the blastocysts are shortened by a sort of accordion pleating. Rabbit blastocysts remain roughly spherical, but toward the end of their free-floating stage (6 or 7 days) they are flabby, like partly filled water bags. By far the handsomest blastocysts I happen to have seen are those of the dog, which are tightly distended with fluid, so that they are truly spherical, under low magnification in a good light they shine like little gems.

The rate of travel through the oviduct and the time required to achieve attachment to the uterine wall also differ from species to species. In most of the known mammals the embryos reach the cavity of the uterus on the 4th day after leaving the ovary. This is true, for instance, of both the mouse and the sow, although the oviduct of the sow is about 40 times as long as that of the mouse. In the dog and cat, however, the journey is known to take about a week. The period during which the embryos lie free in the uterus is also variable. The rabbit's embryo becomes attached on the 7th day, the rhesus monkey's on the 9th, the pig's about the 18th. In the deer, as we have seen, the embryo remains a free and unattached blastocyst for many weeks. In very recent years American zoologists have found a similar condition in three fur-bearing carnivores, the badger, marten, and the weasel, and in an edentate, the armadillo. Every time, indeed, another species is added to the list of which the early development is known, something new or different in form or behavior has been found. When the segmenting ovum and the free blastocyst of the human species become known, we

may be sure that in their own way they will be somehow distinctive.

3

The youngest human embryo which has thus far been discovered is believed to be about $7\frac{1}{2}$ days old. This object, a veritable jewel in the treasury of science, was obtained in 1942 by a Boston surgeon, John Rock, and Arthur T. Hertig, the pathologist of the New England Free Hospital for Women. Its discovery was not altogether a matter of chance, for the two physicians, well aware of the opportunity afforded to science by their busy gynecological service, have been systematically searching for early embryos in uteri which have had to be removed in the hospital, and during the past few years have thus found a score of exceedingly valuable specimens. This particular embryo came from a woman 38 years old, the mother of 9 children. When the uterus came to Hertig's laboratory table, he carefully opened it so as to obtain a view of its cavity something like that shown in Fig. 1. At first he could see nothing, but after the uterus was placed in a hardening fluid he found on the rear wall of the cavity, at the spot marked by a dotted square in Fig. 1, a tiny elevation, barely distinguishable from the surrounding tissues. The photograph at $\frac{1}{5}$ natural size, Plate III, A, illustrates chiefly the inconspicuous character of the embryo—the adjacent picture, B, represents it enlarged $6\frac{1}{2}$ diameters, as Hertig first saw it under his lens. The specimen was then placed in the care of the Department of Embryology of the Carnegie Institution of Washington, at Baltimore, of which Dr. Hertig is a Research Associate. A block of the uterine wall including the embryo was cut on the microtome by Dr. C. H. Heuser into a perfect series of sections 6 microns ($\frac{1}{4000}$ inch) thick. These were mounted as usual on glass slides and stained for microscopic examination. As Embryo 8020 of the Carnegie

Collection the sections are preserved in a fireproof vault in Baltimore.

Fig C of Plate III represents the embryo as it appears in one of the middle sections, magnified 160 diameters. For the benefit of readers who are not accustomed to the biolo-

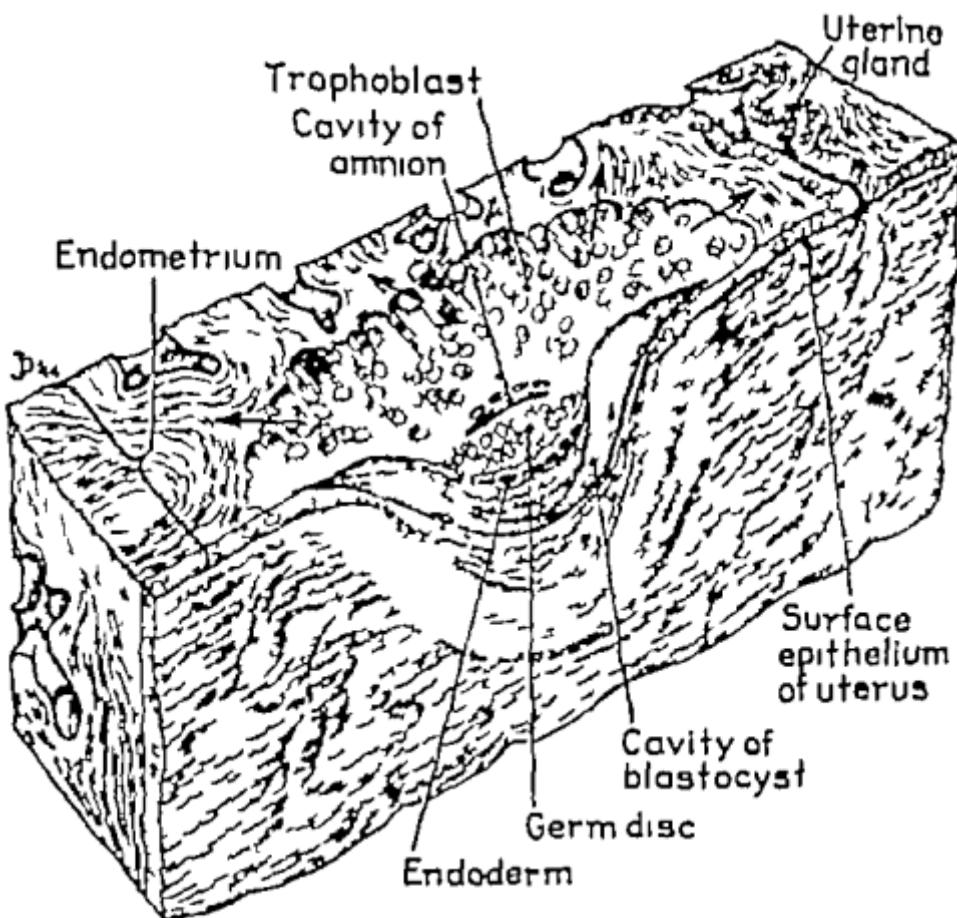


FIG. 8. Schematic representation of human embryo about $7\frac{1}{2}$ days old (Carnegie 8020) drawn by J. F. Dikusch from sketch by author. The embryo is shown as if cut in two as it lies imbedded in the wall of the uterus, only the lower half being illustrated. The upper exposed surface is approximately that of the section in Plate III C. In this drawing the width of the cavity of the blastocyst has been exaggerated for the sake of clearness. Arrows indicate growth of the trophoblast into the lining of the uterus (endometrium). Magnified about 185 diameters.

gist's art of imagining things in three dimensions from flat sections, I have provided (Fig. 3) a sort of 3-dimensional view which cuts the embryo in two like a grapefruit and shows the lower half imbedded in the uterus. The imaginary cut surface at the top is the plane of the photographed section.

It is evident that the embryo is really a blastocyst which has passed a little beyond the simple stage already shown in the mouse and monkey (Plates I and II). It is a hollow structure, not spherical as in the mouse, nor tubular as in the pig, but flattened like a covered bowl. It is no longer free in the uterus, as it must have been until a day or two before, but is three-fourths buried in the uterine wall. The uncovered part of the blastocyst is made of thin cells like those of the monkey embryo in Plate II but that part which is sunk in the uterus is already several cell layers thick and is obviously growing into the maternal tissues. This thickened part is in fact destined to be the means not only of attaching the infant to the mother but of procuring nourishment from her tissues. This we shall explain later, but meanwhile it will be convenient to give this part of the blastocyst its technical name, *trophoblast* ("nourishing germinal tissue")

The cavity of the blastocyst is not conspicuous in the photographed section, for it has been diminished by a process of flattening not known in many other species. In the pen sketch the cavity has been exaggerated (re-distended, so to speak) for clearness. A typical inner cell mass projects into the cavity. In this clump of cells there is a small space, the future *amniotic cavity*, next to the trophoblast, and there is a cap of new cells, slightly different in appearance from the rest of the cell mass (from which they were evidently formed) on its inner surface next the flattened cavity. This is the rudiment of an inner layer of cells which will play a prominent part in the future of the embryo. A similar layer, already beginning to spread beyond the inner

cell mass onto the inside of the adjacent trophoblast, is seen in the monkey's blastocyst (Plate II, B)

4

In order to understand completely the early human embryo and afterward to assess its points of resemblance and dissimilarity to those of other species, we should have to follow through the earliest stages of many other mammals. Both the writing and the reading of this chapter would be easier if we could avoid such a task by taking one "typical" species as a standard—a sort of yardstick by which to measure human peculiarities. There is, alas, no such type. Whatever the original ancestor of all the mammals may have been as an embryo, all of its descendants have deviated in various ways, even at the early stages we are now about to discuss. We should, however, plunge into hopeless confusion amid a stack of treatises on each species if we tried to make our comparisons with each species separately, saying "in this trait a human embryo is like the monkey in that, it resembles the pig or the rabbit." To save time let us frankly set up an arbitrary standard by selecting from among all the various species the simplest or the most explanatory details, combining them into diagrams that will best help us understand the unfolding, complicated as it is, of an embryonic

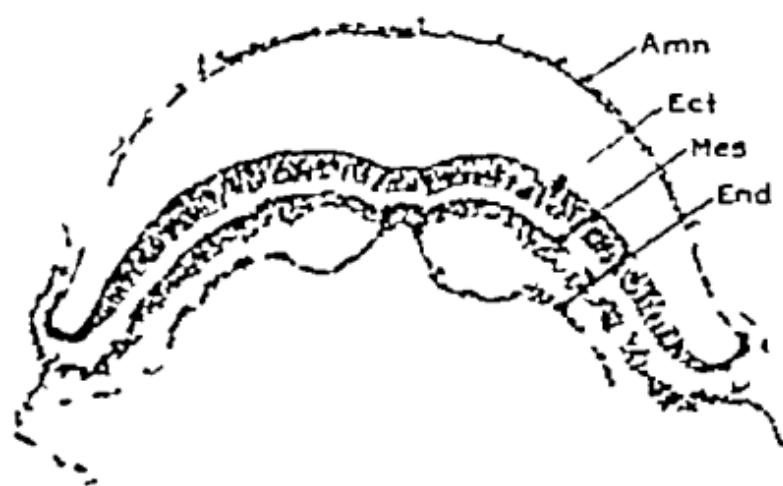
DESCRIPTION OF PLATE III

A, B C, human embryo of $7\frac{1}{2}$ days (Carnegie Collection, No. 8020) A, rear wall of uterus, about $\frac{1}{2}$ natural size. Implantation site is seen as a tiny dot indicated by arrow B Implantation site, magnified about 6 $\frac{1}{2}$ diameters. C, a section through middle of embryo, magnified about 200 diameters. This same section is represented as the upper surface in text Fig. 8, which will serve as an explanatory diagram of this photograph. Courtesy of A. T. Hertig and John Rock.

D cross section of human embryo about 16 days old (Carnegie 5960) illustrating amnion and germ layers. Amn., amnion; Ect., ectoderm; Mes., mesoderm; End., endoderm. This is the embryo shown in Plate VIII A. Magnified about 110 diameters. Courtesy of C. H. Heuser



C



D

PLATE III

ship between widely different kinds of animals than this appearance of a yolk sac in mammals. Every student of nature must assume it to mean that all the vertebrates had a common ancestor which reproduced itself by means of externally laid eggs richer in yolk than those of mammals. This is indeed one of the clear pages in the embryonic archive. But the yolk sac is no mere historical exhibit—it belongs to a living organism. Even though it comes into being through the persistence of an ancient inheritance, it is part of a creature which has to make its living continuously and in narrow quarters. There is no room for ancestral relics. The yolk sac must be put to a new use or disposed of promptly. We shall see what happens—but meanwhile the embryo is growing as we talk.

The next advance we have to consider is indicated at the top of Fig. 4, C. The inner cell mass, which has been flattened into a disc (germ disc) between amniotic cavity and yolk sac, is beginning to settle, so to speak, farther into the center of the blastocyst, and a circular fold of trophoblast is rolling up all around and over it. To understand this, the reader must imagine the diagrams in the round—suppose yourself, for instance, looking down through the ever narrowing drawstring of this fold, onto the upper surface of the germ disc—see Plate IV, B, which illustrates the same process in the pig.

When the folds meet and close, we have then a cavity

DESCRIPTION OF FIGURE 4

FIG. 4 Conventionalized diagrams of the development of a mammalian embryo and its membranes. Explanation in text. In B and C the cells of which the blastocyst is made are shown diagrammatically; in the other diagrams the structures are represented by lines only to simplify the figures. For the same reason, the uterine walls are omitted in B, C, D, E. The small ovals and twig-like outlines in the yolk sac and allantoids of D, E, F represent sections of blood vessels. All., allantoids; Am., amnion; Y.S., yolk sac.

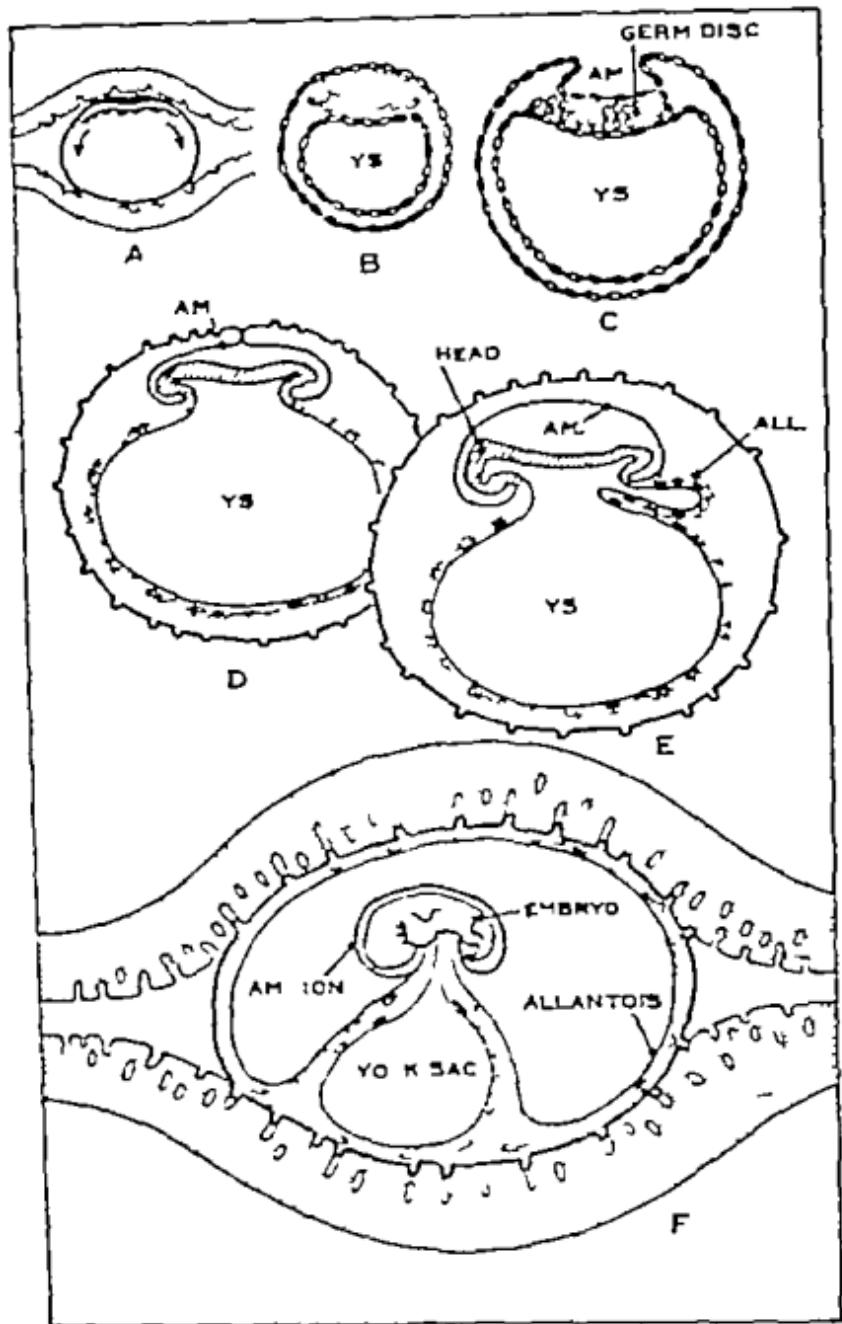


FIGURE 4

above and about the germ disc, roofed over by a new membrane which is called *amnion* from Greek *amnos* lamb named, no doubt, in some ancient sheepfold when the ewes were giving birth. As shown in Fig 4, D, the place of closure of the amniotic fold may persist as a temporary connection in the pig, for example, it holds on for a few days as a tough little string, a quarter inch long, but finally it breaks off.

And now the germ disc is turning itself into something with a head and tail and a gut space that will later be stomach and intestines (Fig 4, D, E). These are the first obvious signs of the prospective body of the new mammal. All the rest—trophoblast, amnion, yolk sac—will serve only for intra-uterine nourishment and protection and will be cast off at birth. From this point on, the word "embryo" will therefore be used to denote the embryonic body, instead of the whole product of the ovum as heretofore.

The fluid filled amniotic cavity now expands all round the embryonic body, something like a loosely inflated balloon settling over it, and the space within the amnion keeps on growing until the embryo floats up in it and is thus almost surrounded by fluid and is protected from shock and from the flattening-out of its jelly-like tissues by their own weight. (See the later stages in Fig 4 and the photograph, Plate IV, A.)

At the stages shown in Fig 4, B and C, the embryo consists of two cell layers as already explained, namely the *ectoderm* ("outer layer") comprising the germ disc and the trophoblast, and the endoderm. During the second week a third layer of cells makes its appearance between the ectoderm and endoderm, as indicated by dashes in the diagrams D, E, and F of Fig 4. This new layer is called *mesoderm* ("intermediate layer"). As the embryo and the membranes grow the mesoderm spreads out into the spaces of the original blastocyst cavity which are not occupied by embryo,

amniotic sac, and yolk sac. The three layers are very clearly shown in Plate III, D, photographed from a human embryo.

From these layers all the tissues of the body are derived. It is roughly correct to say that the ectoderm gives rise to the outer skin and to brain, spinal cord, and nerves—the endoderm gives rise to the digestive tract (stomach, intestines, liver, pancreas, etc.) and to the respiratory organs—the mesoderm provides the skeleton, muscles, heart, blood vessels, and connective tissues. All this is set forth in any good encyclopedia under "Embryology" and more fully in the textbooks, where the reader if interested may pursue the subject. The point of present interest for us is the sequence of development first one cell, then a blastocyst of one layer, then the two-layered (bilaminar) blastocyst, and finally the embryo of three layers. Long ago the zoologists noticed that the whole animal kingdom can be arranged in a similar sequence. There are animals of one cell only, the protozoa. Other low forms, including the coelenterates (e.g., hydras, corals, sea anemones, jelly fish), are made of cells in two layers, an outer skin and a digestive lining. All the other animals have tissues derived from three embryonic layers. Creatures as diverse as the segmented worms, molluscs, crustaceans, and insects develop (in their embryonic stages) three layers—no more, no less—which are recognizably similar to those of the vertebrates in the way they contribute to the various tissues and organs of the adult. It follows from this that all the animals of greater complexity than the protozoa and coelenterates go through some sort of one-layered and two-layered stages in their embryonic history. Many of them develop bilaminar blastocysts so much like those of the mammals that anyone would recognize the resemblance. This is one of the numerous facts which support the so-called Biogenetic Law that higher animals in their various embryonic stages tend to resemble

the embryos of lower forms which is only explainable if we suppose that each species as it develops builds upon a foundation of structure which it inherited from its ancestors. The mammal, when it is an egg, resembles in its unicellular character the egg stage of all lower animals, when it is a bilaminar blastocyst it resembles in that respect the embryos of other mammals above the protozoa. When it is a trilaminar embryo, it resembles the embryos of lower trilaminar animals for example, a mammalian embryo like those shown in Fig 4, E, and Plate IV, D, in which the embryonic body is spread out along the top of the yolk sac, in the watery environment of the amniotic cavity, is definitely similar, in more details than can be shown here, to a young fish or amphibian embryo (see Plate IV, D, E) But all this is probably well known to many readers and is mentioned now simply as a background for our subsequent discussion of early human embryos.

During the first few days after the arrival of the blastocyst in the uterus, it lies free in the uterine cavity. Because it is very minute, its needs for food materials and oxygen can be met from the small amounts of these substances that are present in the maternal environment and which pass into the blastocyst by diffusing through its walls. As it grows, however, it comes under the compulsion of the mathematical law that the surface available for diffusion increases as the square of the diameter, while the bulk of its tissues which must be nourished grows as the cube. Obviously a larger and more efficient surface of interchange must be provided. Soon, therefore, its outer layer, the trophoblast, comes into contact with the lining of the uterus, in some such way as shown in Fig 4, A. Thus begins the attachment of the embryo to the mother. What happens thereafter is extraordinarily different in the various kinds of animals. In some, for example the pig, the trophoblast simply applies itself, as it balloons out, to the inner surface

of the uterine tube, so that whatever nutritive substances are made available by the lining of the uterus are received directly into the trophoblastic wall (see Fig. 18, A) In the majority of animals, however, the outer layer of the blastocyst develops more intimate contact with the mother by means of branching outgrowths or even complex labyrinths (constructed something like the honeycomb radiators of motor cars) which push their way into the maternal tissues as the roots of trees push into moist and fertile ground, seeking nourishment (Fig. 18, B, C) Such an organ of attachment is called a *placenta* (Greek *plakus* a flat cake, from the shape of the full term human placenta) The different types of placentation are of great importance for the classification of animals and we shall see later that there is much to be learned from the human placenta about the place of man among the animals

Consider the situation of an embryo enclosed in a trophoblast shell, such as that represented by Fig. 4, D and E, which has just begun to establish contact with the uterine lining It is rapidly becoming too large and complex to depend upon simple inward diffusion of nutritive solutions through the outer membrane, and its need to obtain oxygen also calls for a more efficient service of supply This difficulty is met by the development of the heart and a system of blood vessels which provide a circulating blood stream to bring foodstuffs and oxygen from the zone of contact with the mother, carry them throughout the growing embryo, and take away the wastes for disposal into the maternal blood.

The first blood vessels take form in the mesoderm which has condensed on the yolk sac and within the embryo This fact probably has its place in the historical archive let us imagine the primitive protomammalian embryo compelled by some evolutionary crisis to adjust itself to life within the mother, unlike its kin which have always developed in

the water. It is already provided with a yolk sac containing nutrient yolk, and with blood vessels from the yolk sac to the embryonic body for the transport of foodstuffs. The yolk sac is moreover the most prominent part of the total creature and the most likely means of making contact with the uterine lining. We can easily imagine it settling into contact and so placing the blood vessel network in close apposition to the uterine surface. Thus we have the beginnings of a placenta. As the evolutionary process went on, the need for actual yolk would disappear because food was being filtered in directly from the mother, but the yolk sac, now useful in this new way, would persist.

This is only a conjecture, for the whole page of nature's archive at this point is torn out, but it is a fact that in many mammals the yolk sac makes functional contact with the inside of the trophoblast shell, as indicated in Fig. 4 at bottom of diagram F, thus creating a yolk-sac placenta. The blood vessels of the yolk-sac wall grow into processes of the trophoblast which interlock with the uterine lining, and nutrients and oxygen filter through the thin blood-capillary walls into the flowing blood and are carried to the embryonic body for use.

If that were the whole story of the placenta, this chapter would be sooner done. It seems that the yolk-sac placenta proves to be not entirely adequate, for in every placental mammal (the marsupials do not enter this discussion) there is some sort of further addition to the placental system, until indeed the placenta becomes the most varied of all the organs of the animal body and the most difficult to understand and explain. The placentas of mouse, elephant, and man, for example, are more different from one another than the brains or even the noses of the same three species.

To begin with, the yolk-sac placenta is always transitory or limited in extent. In a great many species it is supple-

mented and usually superseded by a curious structure, the *allantois* (Greek *sausage like* probably because of its enormous size and swollen, elongated shape in the pig). This is a sac-like outgrowth from the endodermal rudiment of the gut canal in the tailward part of the embryo (see Fig. 4, E, F, all., and Plate IV, C). That part of it which is within the embryonic body ultimately becomes the urinary bladder. It grows out and expands in all directions, billowing over the amnion, crowding inwardly against it and outwardly against the yolk sac. If the reader has difficulty visualizing this explanation of the allantois, let him insert a child's sausage-shaped rubber balloon into a paper bag and blow it up until it fills the whole space. If there are a couple of oranges in the bag, representing the amniotic sac and the yolk sac, they will be crowded and closely overlaid by the rubber membrane. The allantois, issuing as shown in Fig. 4, F, from the caudal end of the embryo, fills all the available space and presses into intimate contact with the inside of the trophoblast shell. As it grows out of the embryonic body it picks up a coating of the mesodermal tissue through which it pushes, and is thus provided with the "makings" of blood vessels. In this way allantoic blood vessels reach the farthest part of the trophoblast shell and enter the tissues of the placental attachment.

The allantois is not peculiar to the mammals. It is a regular feature also in the embryology of reptiles and birds, in which it serves chiefly as a respiratory organ, a kind of lung if you like spreading out its blood vessels over a large area of the inside of the shell, and there taking up transpired air for use of the growing embryo. The allantois is thus an important item in the historical archive of the embryo and is to be counted among those facts which suggest that the birds, reptiles, and mammals have a common ancestral history.

I must emphasize again that the story of early development just given is only a simplified diagram. There is no one animal with a history just like this, and in fact every single feature may be and is different in one or another species. We can say without reserve only that all mammals arise from one-celled eggs, pass through a blastocyst stage, and thereafter develop the embryonic body from a disc on the floor of an amniotic cavity within an outer trophoblastic shell. These fixed items present themselves, however, in an infinite set of variations. The time-schedule of development is not the same in any two species—the blastocyst takes various shapes—the amnion forms in a variety of ways—the yolk sac may be large or small, closed or open, functional or atrophic, in some of the rodents it turns itself almost inside out—the allantois may be absent, small, large, immense. The effort to analyze all these diversities and to get some sort of meaning out of them—to use them if possible to learn more about the interrelationship of the various orders and families of mammals—has become a special branch of biology, of astonishing complexity and difficulty. The jungles and hillsides of the world must be ransacked for out-of-the-way species which may fill the many gaps—embryos of squirrel and rabbit, sheep and dog must be set beside those of macaque and armadillo and of unheard-of creatures from distant lands like the tarsier, tenrec, and tupaia. The most skillful arts of the microtomist, optician, photographer, and draughtsman must be put at the command of analytic science. At the focus of all this effort stands our own species, whose earliest embryos are scarce and inaccessible not because of distance or rarity but because they come to the laboratory only through the hands of the surgeon, as by products of human distress and the urgency of the operating room. In the laboratory where these words are being written, 9,000 human embryos and fetuses have been entered in the record books each one with its history of frus-

tration and its challenge to new discovery, each an honored and cherished gift upon the altar of truth

5

Let us now attempt to sketch the development of the human embryo during its second week, and on to about the 16th day, as far as can be done from present evidence. The material for such a study consists of about two dozen specimens, of which one-fourth have been obtained by Hertig and Rock and are in the Carnegie Collection in Baltimore, the rest being at various laboratories in Europe and America. The earliest (Carnegie 8020) has already been described above and from it we have learned that like all the other mammals man goes through a blastocyst stage. This statement will hardly startle present-day readers, prepared as most of them are to recognize our own species as one among the animals but it is something which has had to be proved against a contrary hypothesis. Until a decade and a half ago, it must be remembered, nothing whatever was known about the embryology of man earlier than about 15 days. The earliest specimens then at hand were just enough different from the species of which the early development was well known to be very puzzling. My professional colleagues will think of the Peters embryo, of the Teacher-Bryce embryo which the late J. H. Teacher kept in a safe in his own house in Edinburgh, and a few other specimens of about the same age, some of which we now know were abnormal or badly preserved. Studying them, it was not evident how they could have developed from a typical blastocyst stage, and it was supposed by some very good embryologists that the human embryo must continue in the solid (morula) form without hollowing out into a blastocyst, and only much later at 10 or 12 days perhaps develop its amniotic sac and yolk sac in some none-too-clearly envisaged way. One such conjecture, that of von Möllendorff (1926),

is shown in Fig. 5, E for comparison with the factual diagrams in Figs. 3 and 5, D. There is an ever-present tendency to represent mankind as different from the beasts, not only because of religious doctrines but also no doubt because of unconscious pride in our own species, which may lead even biologists to expect something peculiar in human structure.

Already, however, a few early embryos of several kinds of monkeys had been described by the great Dutch embryologist Hubrecht and by the German Emil Selenka. From these the existence of a blastocyst stage in primates other than man was known, and was built into a theoretical picture of human origins in a distinguished Croonian Lecture given before the Royal Society of London by J. P. Hill in 1932. In 1923 the Carnegie Embryological Laboratory began systematic collection of embryos of rhesus monkeys by breeding them in a laboratory colony, as a joint enterprise of C. H. Hartman, G. L. Streeter, and C. H. Heuser. By 1938 Streeter was able to describe, with superb photographs, four monkey blastocysts 8 and 9 days old, showing that this particular primate, obviously much like man in many ways, possesses a blastocyst so general in its structure that it could safely be used to exemplify a typical mammalian blastocyst. Finally we have the evidence of the early human embryo described above (Carnegie 8020, Plate III and Fig. 3). This is authenticated as a normal specimen by the evidence of others, slightly older, next to be described and it proves the existence of a blastocyst stage in man. Admittedly this particular blastocyst has already entered the period of attachment, and we cannot know what it was like in the free-floating stage. Earlier specimens are greatly to be desired, but we already know enough to avoid any further risk that prideful or mystical thinking may separate our own species radically from its fellow creatures.

The reader may, however, have noticed that the human

blastocyst thus seen on or about the 8th day is quite different in at least three details from the comparable stage of our synthetic mammalian embryo of Fig 4 (1) on the side toward the uterus the trophoblast is greatly thickened, forming an invasive mass of cells which is already spreading into the tissues of the mother (2) the embryo is deeply imbedded in the uterine wall, being two-thirds buried there, instead of merely becoming attached to the surface by contact (3) the amniotic cavity is being formed early by a process of the trophoblast splitting apart from the embryonic disc instead of folding over it. The first of these features, namely precocious growth of the trophoblast, is (I believe) unique in degree among the known mammals, a fact which may comfort those who crave distinctiveness for man but the rhesus monkey shortly develops something of the same sort and the great apes are yet to be heard from. The other features, the subsurface (interstitial) implantation and amnion formation by splitting away or "cavitation," are characteristic of certain other mammals.²

Until we see the human blastocyst in its free state, we may permit ourselves a cautious guess that its progress before implantation must be a good deal like that of the rhesus monkey Fig 5, A to C, shows diagrammatically the early attachment of the monkey blastocyst up to the stage it reaches at 10 days (C). The human embryo must be something like this but at an earlier time about day 7. By day 8, if Carnegie 8020 is correctly dated, it has already burrowed much deeper (Fig. 5, D) than in the 10-day monkey. It is generally supposed that when the early embryo invades

2. I do not wish to overemphasize the differences between these modes of amnion-formation; further research may perhaps reveal a fundamental similarity in principle, between the movements of cells which result in producing the cavity whether by folding or by splitting (cavitation); but the observable modes are certainly as distinctive as many of the anatomical characteristics of adult animals upon which taxonomic classification is based.

the maternal tissue, as it does to various degrees in man and the chimpanzee, the guinea pig, the gopher, the European hedgehog *Erinaceus*, and some other species, it does so by action of some sort of digestive ferment elaborated by the trophoblast.

During the second week the development of the human embryo is quite different in certain details from that of most of the other mammals. Without a running explanation the reader might strive in vain to understand the diagrams of this period (Fig. 6) in terms of the generalized plan of Fig. 4. Fig. 6, A, represents a section of another of the Hertig Rock embryos, Carnegie 7699. It is about 11 days old. The maternal tissue of the uterine surface is growing over the implanted embryo and will soon cover it. At the same time, the trophoblast continues its precocious activity, creeping outward in all directions and eroding away the maternal tissues with which it comes in contact. This enormous increase of the trophoblast is the most striking feature of early human development. As the trophoblast grows it becomes cavitated with irregular spaces called *lacunae* which become filled with more or less stagnant blood from small maternal veins (not shown in the diagram) that are opened by the advancing trophoblast. From this blood it

DESCRIPTION OF FIGURE 5

FIG. 5 Diagrams A, B and C illustrate three stages of the attachment of the rhesus monkey embryo, by Wialocki and Streeter from specimens in the Carnegie Collection. A free blastocyst, 9 days old; B blastocyst in contact with lining of uterus, 9 days; C, 10 days; note trophoblast (solid black) eroding the surface layer of the endometrium. D represents the human embryo at its earliest known stage (Carnegie 8020, 7½ days). The blastocyst has already become implanted below the surface of the endometrium.

The six small diagrams above the letter E illustrate a hypothetical explanation of the early embryology of man, proposed by a European embryologist before the specimens illustrated in A to D were known. They are shown to emphasize the recent advances in knowledge of primate embryology.

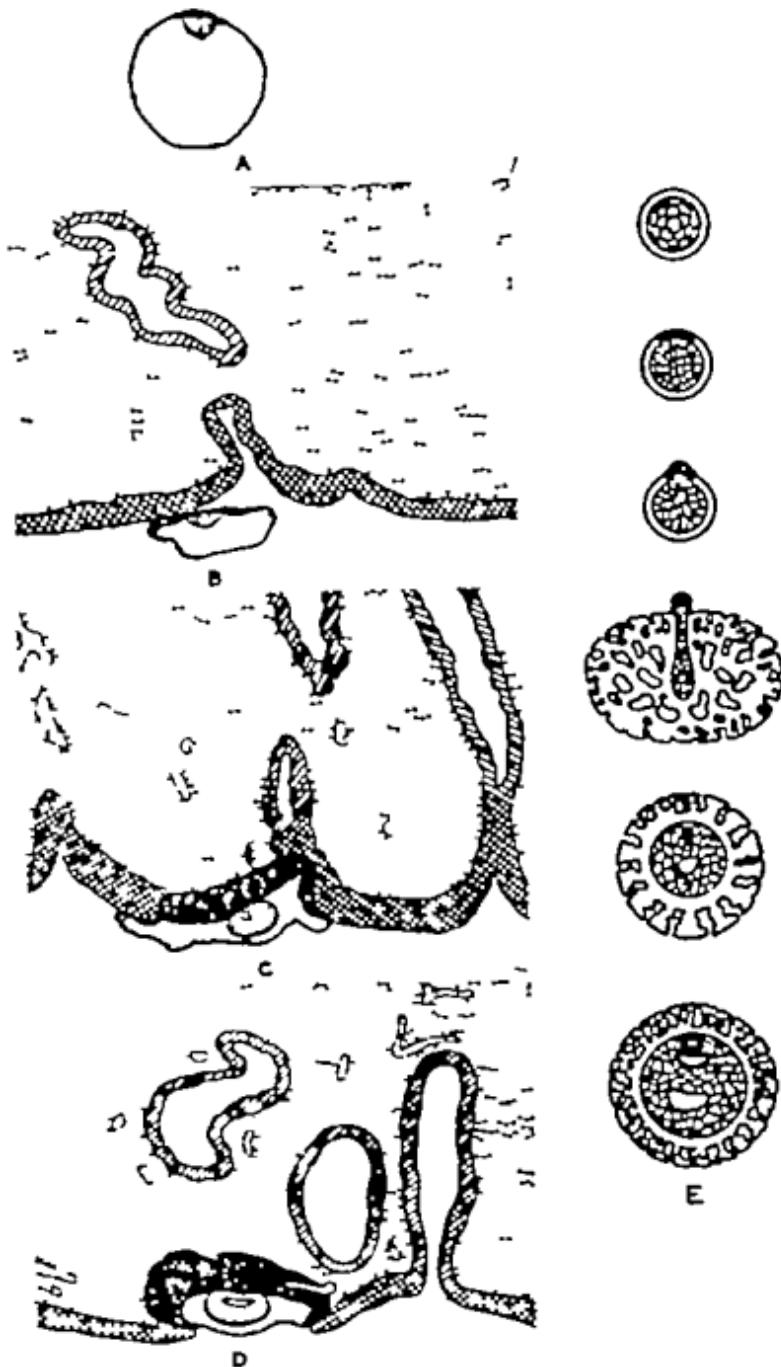


FIGURE 5

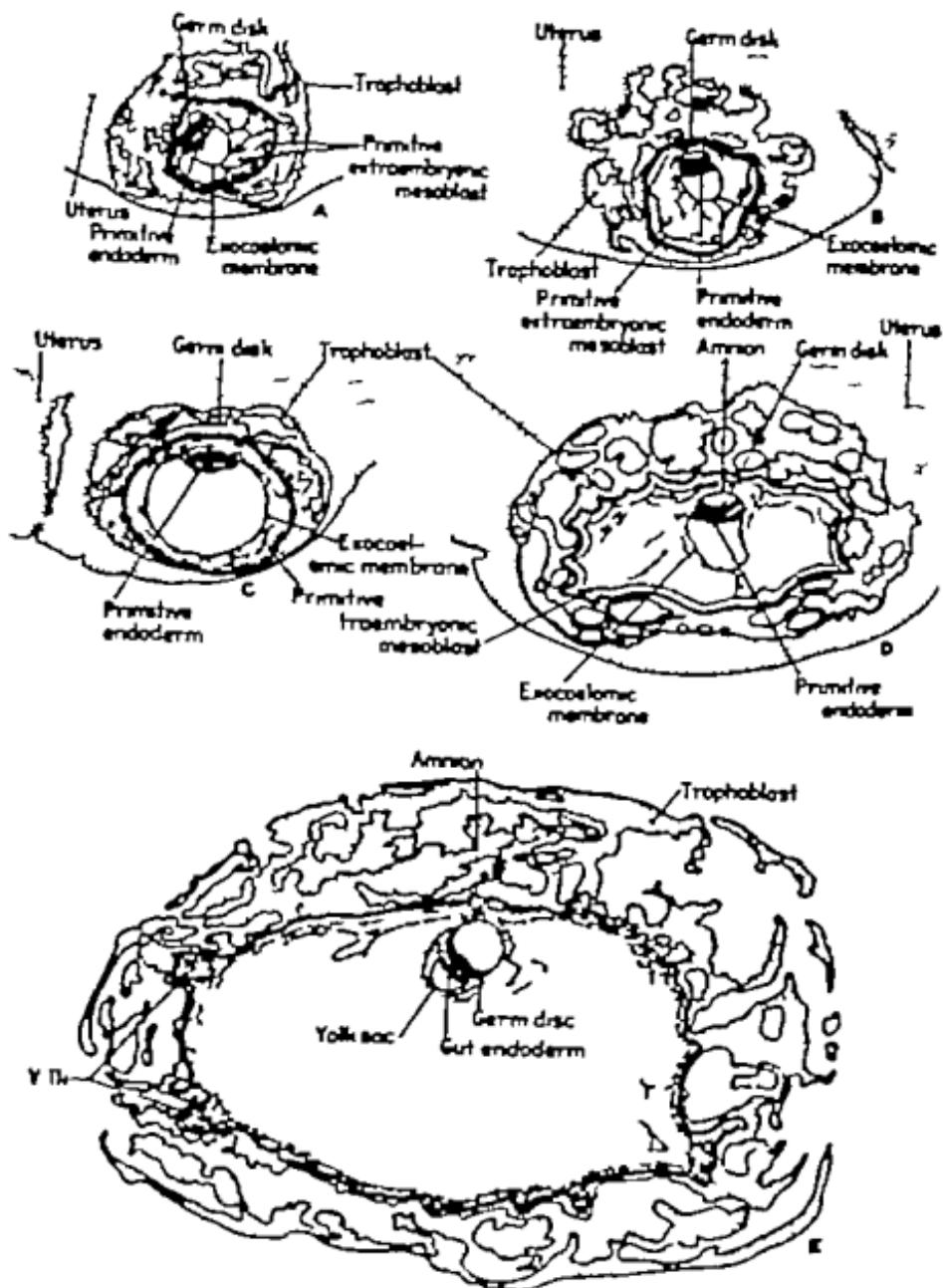


FIG. 6. Diagrams of sections of early human embryos, showing the development of amnion, yolk sac, primitive mesoblast, trophoblast, and villi. The lacunae mentioned in the text are represented by white spaces in the diagonally shaded trophoblast. A, 11 days (Hertig-Rock, Carnegie 1589); B 11+ days (Miller Streeter Carnegie 4900); C, 12 days (Hertig-Rock, Carnegie 7700); D 12+ days (Werner-Stile); E, about 18 days (Edwards-Jones-Brewer). All magnified 80 diameters. From the *Carnegie Contributions to Embryology* by courtesy of Arthur T Hertig and John Rock.

presumably extracts material for the embryo. Within the trophoblast shell there is a germ disc derived from the inner cell mass like that of other animals. Above this disc the amniotic cavity, which began as a tiny cleft between the inner cell mass and the trophoblast, grows larger and the cells of its roof form a definite layer. The endoderm cells spread out to form a circular plate below the germinal disc so that we have a bilaminar embryonic body forming region of ectoderm and endoderm as in other animals (compare Fig 4, C). The endoderm does not, however, simply line the inside of the trophoblast shell in a single layer, as is common in other animals. Exactly what does occur at this stage is not yet clear, for the series of available specimens is too sparse to give us all the details. Already at 11 days (Fig 6, A) we see that a few cells are moving from the region of the embryonic disc out into neighboring regions of the blastocyst cavity. Soon afterward (Fig 6, B) the cavity becomes lined or partially filled with a loose network of new cells, leaving a reduced inner space roofed with endoderm and walled by a thin membrane of the loose cells. Since this delicate inner sac is something new to science and has had to be named quite recently, in the Carnegie Laboratory we often refer to it as Heuser's membrane, because our colleague C. H. Heuser was the first to emphasize its existence. In the diagrams, however, it bears the more formal name *exocoelomic membrane*. In a few days it becomes thicker and more sharply defined and thus forms a small yolk sac (Fig 6, D).

Just how to correlate this spongy inner tissue with the time-honored three-layer system is at present a puzzle to the specialists on primate embryology. Part of it appears to enter, as already stated, into the formation of the yolk sac wall. Shall we then call it endoderm, even though it does not resemble the characteristic endoderm of the embryonic disc? On the other hand, the rest of it behaves like connective

tissue (mesoblast), which suggests that we classify it as mesoderm, but then we must admit that it arises precociously, before the yolk sac is complete. The labeling of our diagrams gives preference to this interpretation, calling it *extraembryonic mesoblast*. For the time being let us leave the experts to lose sleep over this problem its importance for us, and the only reason for burdening the reader with so technical a question, is that this particular sequence of events has been seen in two species besides man it occurs in the rhesus monkey, and is known by reasonable inference to occur in the chimpanzee. These three are the only primates whose very early blastocysts are known All three are alike in this striking particularity, differing thereby from mammals of all other orders. In one other species only has something like it been described, and that too is related to the apes and monkeys, namely, Galago, one of the African lemurs. In the primitive primate Tarsius, and in the South American (Platyrrhine) monkeys a somewhat later but still relatively precocious origin of the extraembryonal mesoblast is known to occur On this page of the archive of the embryo, then, is written large and clear the record of a common origin, ancient though it may have been, of man and ape and monkey

6

I hope that the human being whose biography during the first weeks of life is being sketched herewith, is already something more to the reader than a diagram in a book. This is your history I am telling and mine, and that of my own child and of yours. Here in the laboratory we can of course study and depict for you only those whose lives have been interrupted, and yet our experience trains us to think even of them as witnesses of life and growth. They never seem to us static or defunct. I have heard an embryologist who thought himself unsentimental and impersonal talk affec-

tionately of a handsome three-weeks embryo as "he" and speaking for myself, I seldom sit at the microscope to study one of these individuals we call "specimens" without the thought that here is one who but for the turn of circumstance would have taken his place in the army of the living. A microscope slide, says Professor W. B. Cannon, is a frozen moment in the flux of life.

Realize, then that man even in his earliest weeks faces unconsciously the unending problem of getting along in his world. Life is a paradoxical career in which the individual must both accept and contend with his environment, at once struggling for independence and adapting himself to co-operative action. Before birth this effort and adjustment are a matter of physiology alone; only later is the struggle complicated by problems of mentality and social custom and by those workings of the spirit through which a man must pilot his individual life to success or failure in his community, to achievement or martyrdom, to turmoil or inward peace. For the embryo in the uterus, pilgrim's progress begins with the process of attachment or placentation, by which the human child is to win his nine months of prefatory life. Thus early must he contend with his environment—which for the time being is the lining of his mother's uterus—and at the same time must adjust himself thereto.

There is no way I can make clear what the reader must next assimilate if we are to reach instructive conclusions, without describing the microscopic anatomy of the uterus and of the placental attachment between mother and child. It is never easy to convey in nontechnical terms an idea of the finer structure of the tissue of the human body but embryology without cell structure would be worse than a travel book without a map. Let us therefore buckle down together for a few pages and try to build up (for subsequent use) a picture of the intimate structure of the uterus and especially of its lining membrane, the *endometrium*.

The effort would be much easier if we could sit down together in my laboratory and prepare a specimen as shown in Fig. 7. Taking a preserved human uterus from a jar of formalin we cut it in two, lengthwise, with a sharp knife so that we can look into the cavity, Fig. 7, A. The organ consists of an outer pear-shaped wall of dense involuntary muscle, lined with a velvety internal layer about 5 millimeters ($\frac{1}{8}$ inch) thick. Next, we cut out a horizontal slab of uterine tissue (B) and from this we detach a little block running down through the endometrium into the muscle (C). This we shall place on the table so that its upper side will be that which forms the surface of the lining facing the cavity i.e., like a cube of melon with the rind downward and the pulp upward (Fig. 7, C). After we have studied and sketched it under low magnification we shall cut off a very thin slice (technically, *section*) from one side, stain it with appropriate dyes and photograph it through the microscope (Plate V, A). The uterus of many of the animals mentioned in this book, unlike that of man and the apes, are two-horned as shown in the inset of Fig. 1. When the tubular horns are small, we usually cut our blocks from their whole thickness, as one slices a banana, and therefore the thin sections for microscopic study are round, with the uterine cavity showing in the center (see Plate V, B, in comparison with A of the same plate).

DESCRIPTION OF FIGURE 7

FIG. 7 Block diagram showing structure of the lining of the uterus (endometrium). At A the uterus is represented as if cut in two lengthwise, to show its lining. At B is shown a block cut from the uterus; a small part of this is represented at C, turned so that the inner surface of the endometrium is upward, showing the glands. At D a small part of C is drawn still more enlarged, to show that the glands are cell-lined tubes dipping down from the surface epithelium. At the right side of C the blood vessels of the endometrium are schematically indicated. Slightly modified from *The Hormones in Human Reproduction* by George W. Corner by courtesy of Princeton University Press.

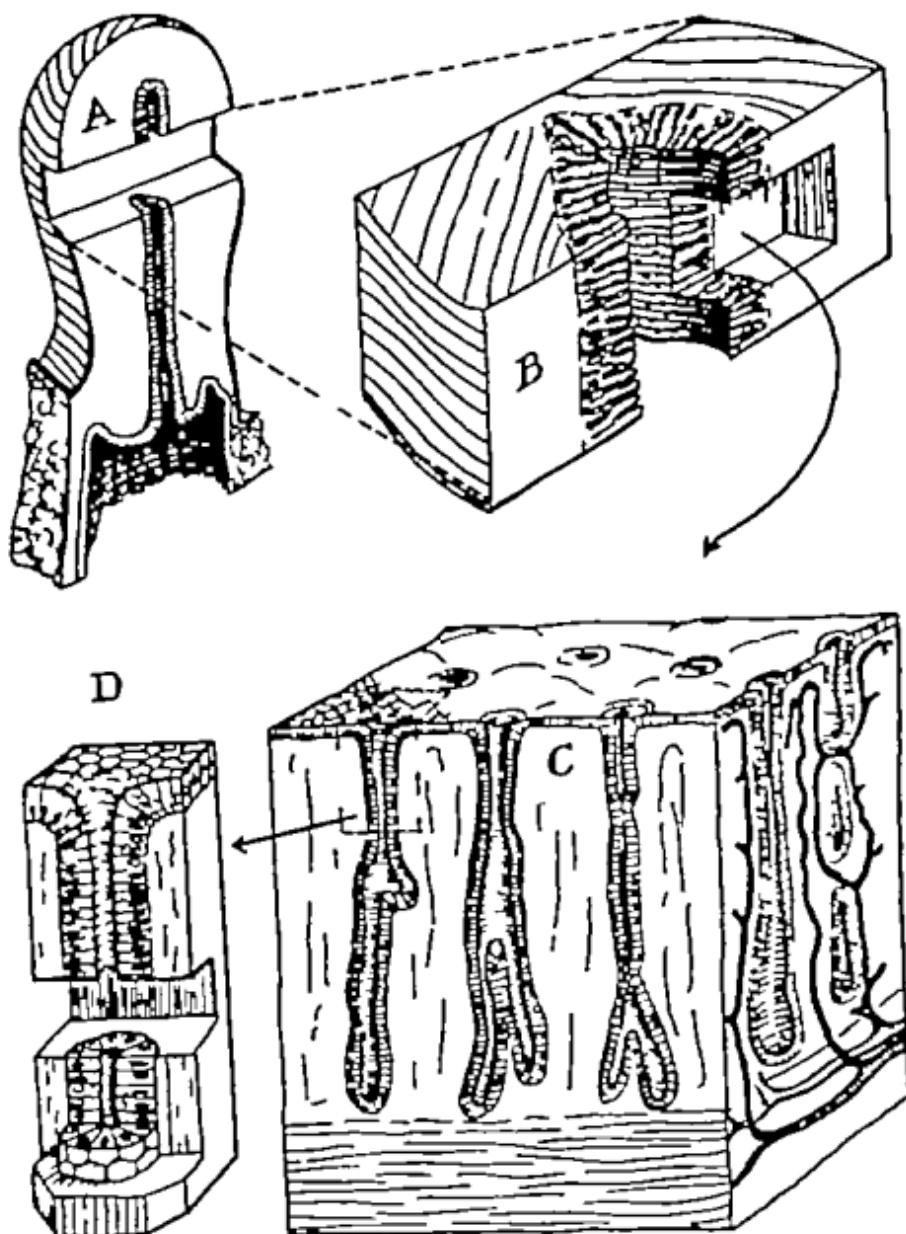


FIGURE 7

We find that the surface is paved with a single layer of tall cells and that at frequent intervals this surface layer pushes down into the depths of the endometrium, forming finger like tubes closed at the ends, which reach almost to the muscle (Fig 5, C, D) These tubes are supported by spongy connective tissue and between them there is a network of capillary blood vessels supplied by arteries, as shown on the right hand side of the block diagram (Fig 5, C) The tubules are in fact glands, able to take water and the "makings" of nutritive substances from the blood vessels, build them up into foodstuffs for the early embryo, and discharge the resultant secretion into the cavity of the uterus. The endometrium may therefore be compared to a quick lunch counter with a supply of raw foods in the rear (in the blood stream), a row of cooks and waiters (the gland cells), and a line of customers (the cells of the embryo) in front. The outfit does not however function in this way all the time, but goes into action when an egg leaves the ovary. Therefore when the embryo reaches the uterus it does not find itself in an indifferent environment, like the Biblical seed that was sown on stony ground. On the contrary, it finds the endometrium in a very particular state of readiness to receive and nourish it. The nature of the pre-

DESCRIPTION OF PLATE V

Preparation of the uterus for implantation of the embryo (progestational proliferation) in human, rabbit, and pig. In each case the left-hand figure shows the interval stage, the right hand figure shows the effect of the corpus luteum hormone. A, this process in the human uterus, from the first description by Hitschman and Adler 1908. Magnified about 14 diameters. B, the first pictures of progestational proliferation of the rabbit's uterus, by Bouin and Ancel, 1910. Magnified about 9 diameters. C, the same change in the uterus of the sow from preparations by the author. The left-hand figure represents the day before ovulation, the right-hand section was taken 8 days after ovulation. Magnified about 9 diameters. From *The Hormones in Human Reproduction* by George W. Corner 1912, by courtesy of the Princeton University Press.



B



PLATE V



A



PLATE VI

paratory changes and how they are brought about at exactly the right time, makes a long and complex story which can only be summarized here. I have recently told it in full in another book written for the general reader.* When the Graafian follicle discharges its egg (Fig. 1) it is promptly converted by modification and growth of the cells of its lining into a special organ of internal secretion, the so-called *corpus luteum* or yellow body. This structure produces a chemical substance (hormone) which is carried by the blood stream to the uterus and there induces a remarkable change in the endometrium. The glands of the uterus begin to grow, to secrete fluid, and therefore to become dilated. Their cells multiply so fast that there is not sufficient room for them in the simple tubular wall, and the glands become folded or pleated. The tissue of the endometrium is deeply pervaded by these glands, and finally in a section of the uterus we see a more or less lace-like pattern (Plate V, right hand panels) representing the cross section of the gland filled endometrium. Direct experiment on animals by removing the corpus luteum in earliest pregnancy has proved that this changed (*progestational*) condition of the uterus is absolutely necessary for nourishment of the free-floating blastocyst and for its implantation in the uterus.

Human embryos of the second week like those shown in

3. *The Hormones in Human Reproduction* (see Bibliography)

DESCRIPTION OF PLATE VI

A, section of human embryo about 12 days old (Carnegie 7802) showing the embryo proper and the placental villi, which are beginning to grow out from the envelope (chorion) of the embryo. Magnified 27 diameters. From *Contributions to Embryology*, Carnegie Institution of Washington, by courtesy of Arthur T. Hertig and John Rock. B C, two views of a human embryo in the chorion (intact at left, opened at right). Carnegie 7598, about 5 weeks old (age from fertilization). The villi are beginning to thin out on the most superficial part of the chorion. Note the yolk sac attached to the belly of the embryo. Magnified about $1\frac{1}{2}$ diameters.

Fig 6 and in Plates III, A, B, C and VI, A, are therefore implanting themselves in endometria fully prepared to receive them.

7

As the demands of the rapidly growing embryo for nutriment and oxygen become more and more exacting, the trophoblast undergoes a further change by which the surface it presents to the maternal blood becomes enormously greater. This new physiological adjustment to the environment, which begins about the 12th day, is well seen in Plate VI. It consists in the formation of fine finger like processes of the trophoblast (called *villi* from Latin *villus* a tuft of hair) which push outward as indicated in the photograph, carrying within them cores of the spongy connective tissue (mesoblast) which, as previously explained, lines the wall of the trophoblast shell. Where the sectioning knife happens to cut the villi crosswise, the cut ends appear as oval or round outlines filled with the lighter mesoblast (see Fig 10).

A glance at the photographs shows also that within the growing cavity of the blastocyst the mesoblast is thinning out but a little stalk of this tissue remains, connecting the two embryonic vesicles (amnion and yolk sac) to the inside of the trophoblast shell. This arrangement is made quite clearly understandable by the little drawing, Fig 8, of the corresponding part of the Lockyer embryo (Carnegie 6026). The mesoblast thus forms a continuous layer lining the trophoblast shell, filling the cores of the sprouting villi, serving as a stalk for the embryo proper, and lightly covering the amnion and the yolk sac. It is obvious that when the first blood vessels begin to develop, as they do very soon, in the mesoblast of the yolk sac and body stalk, they have in this layer a clear road over which to reach all round the trophoblast shell and into the cores of all the villi.

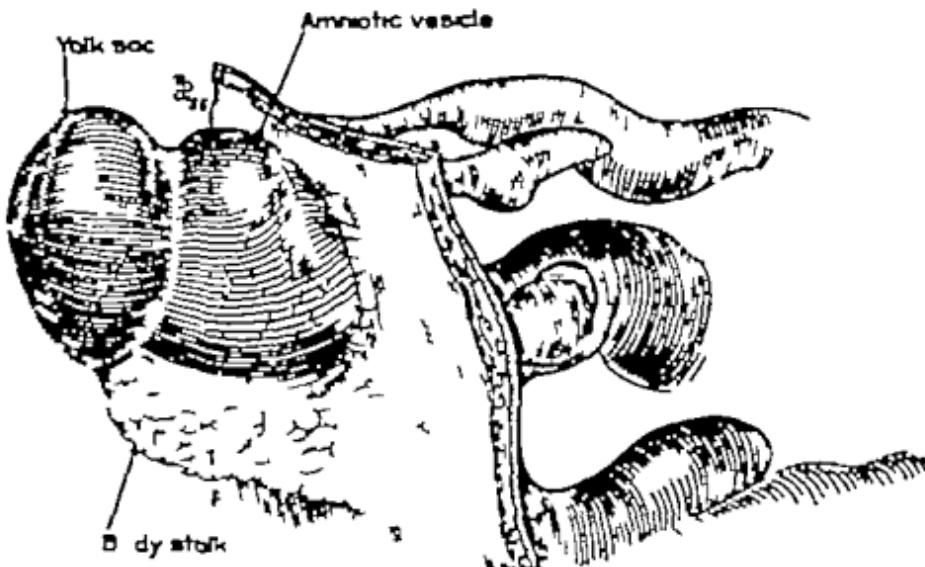


FIG. 8. Part of trophoblast wall with villi and embryo proper to illustrate the way in which the embryo is held to the inside of the trophoblast by the body stalk. To place the specimen in same relative position as in other diagrams of early embryos illustrated in this book, page should be turned to put yolk sac at bottom. Through the mesoblast of the body stalk blood vessels make their way from the embryo to the chorion, thus obviating the need of an expanded allantoid. Human embryo about 18 days old (Lockyer Carnegie 6076) Magnified about 125 diameters. Courtesy of Elizabeth M. Ramsey

For the sake of clarity, it should be said at this point that the outermost layer of the whole embryonic mass, i.e., the trophoblast, now lined by mesoblast, is given the name *chorion* (an ancient Greek word) when it becomes a strong membrane around the well-established embryo. The villi are of course extensions of the chorion. At first they are simple in form, but before long they begin to branch, and ultimately each of them becomes the trunk of an extensive tree-like system.

It is now necessary that we consider events within the chorionic shell. Looking first at Fig. 4, D, and then at Fig. 9, A, we see that the embryonic disc or shield assumes the bodily form of an embryo just as in other mammals, form-

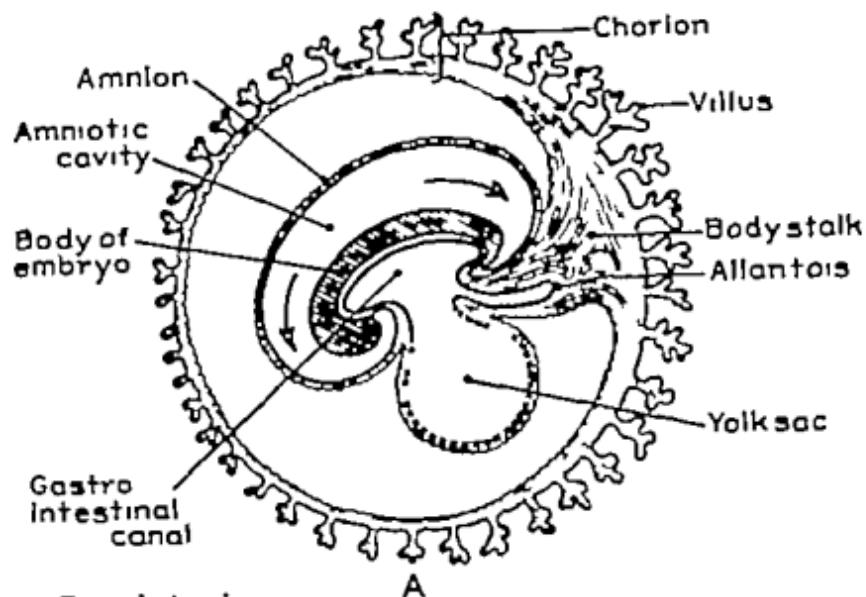
ing itself over an intestinal canal continuous with the yolk sac cavity. The amniotic cavity balloons throughout the chorionic cavity, also as in other mammals, until its spreading walls, as shown by arrows in Fig. 9, B, crowd the neck of the yolk sac against the body stalk, thus forming the umbilical cord. The amniotic membrane also pushes outward, and finally fuses with the chorion (see Plate VII, C).

Because, as already pointed out, the body stalk provides a direct and early route for blood vessels between the embryo proper and the chorion, no large development of the allantois is necessary in man. It never becomes more than a rudimentary tube of microscopic size, in the body stalk. Nor does the yolk sac acquire even a temporary functional contact with the chorion, as it does in many animals (Fig. 4, F). It too remains small and (so far as we know) functionless after the chorionic blood vessels are established. In these details the human species, together with the other Primates, resembles three other orders of mammals, namely the Chiroptera (bats), Rodentia, and Edentata (armadillos). This is one fact among many which suggest that these four orders are grouped as a special branch of the family tree of the mammals.

At first the whole surface of the chorion is covered with villi, but reference to Plate VII, A, will show that the villi on the superficial part, which protrudes into the uterus as the chorion grows, are not favorably placed for survival. They gradually thin out and disappear, except on a disc-shaped area at the base of the implantation. Thus we arrive at the final arrangement of the placenta, shown in Plate VII, C. Meanwhile the bulging side of the chorion crowds against the far side of the uterus and in the fourth month

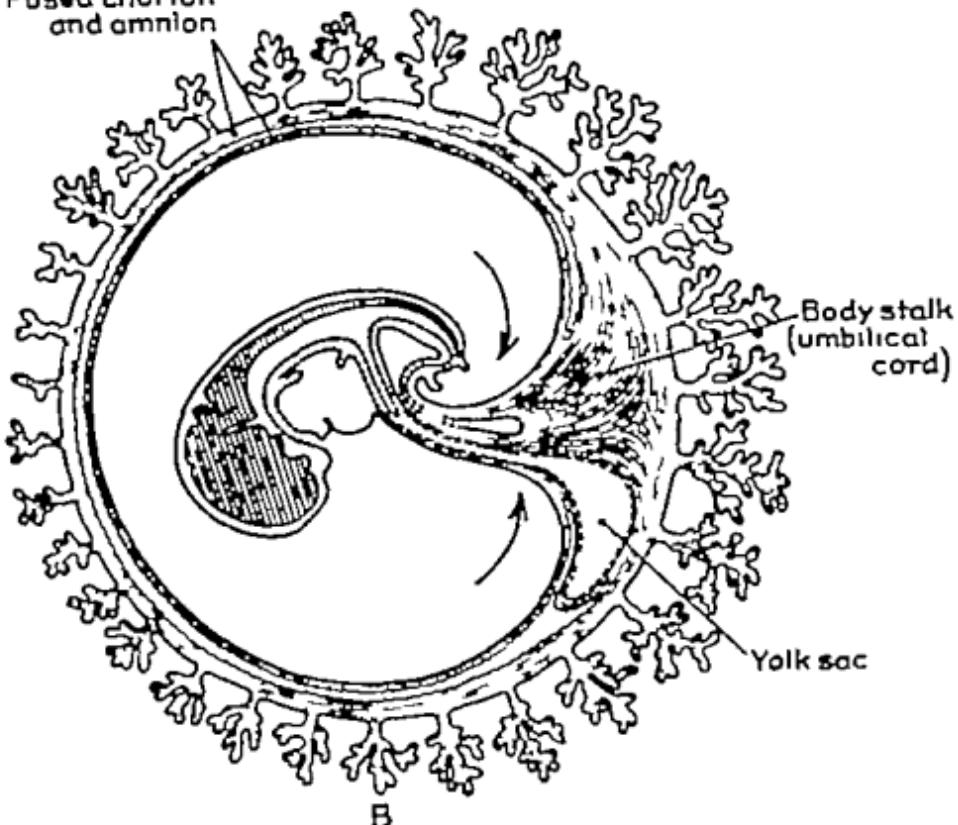
DESCRIPTION OF FIGURE 9

FIG. 9. Schematic diagrams of human embryos illustrating the development of amniotic cavity, yolk sac, allantois, and umbilical cord. Magnified.



A

Fused chorion
and amnion



B

FIGURE 9

of pregnancy it fuses with that wall, obliterating what was left of the uterine cavity. All this is shown in the drawings of the late Max Broedel, Plate VII.

When fully developed, the human placenta is about the size of a small soup plate, that is to say 18 centimeters (7.5 inches) in diameter, and weighs 500 grams (a little more than one pound) on the average. The villi of which it is formed grow into the wall of the uterus, breaking down everything in their path, and destroying the glands, connective tissue, and blood vessels all the way to the muscle. Thus they excavate a space for the placenta in the uterine lining.

If the reader has difficulty visualizing the relation of the placenta to the uterus, let him imagine a piece of ground (representing the uterine wall) beneath which is a network of terra cotta pipes (the blood vessels). Dig a hole in the ground, breaking off the pipes as you dig, and make it just large enough to receive the dense roots of a tree (the placenta). Pave the ground over the hole and all about it, the paving representing the chorio-amniotic surface of the placenta (see Plate VII, C). The trunk of your tree is the umbilical cord. The roots will be bathed in fluid from the cut ends of the underground pipes in like manner the root system of the placental villi dips into a sort of pool filled with maternal blood from the opened ends of small arteries and drained by opened veins. This blood is the source of oxygen and nourishment for the infant and the means of disposal of carbon dioxide and organic wastes which filter back into it from the villi roots of the embryo.

8

The reader is probably beginning to weary of structural detail, but we are coming in a few pages to certain matters of philosophical importance (and more in Chapter III) which will be meaningless unless we visualize the finer structure of the placenta and understand something of the quite

extraordinary differences between the placentas of different mammals.

Next, then, the fine structure of the villus (Fig. 10) Each of the branching rootlets has a core of loose mesoblast covered with a thin but continuous wall of tissue derived from the trophoblast. Within the core run thin walled terminal loops of the blood vessel system of the infant. The blood stream, kept circulating by the infant's heart, flows through the main artery (aorta) of its body and out through the umbilical arteries to the placenta, where it is distributed into the innumerable branches of the villi. Here occur the exchanges of soluble substances from and to the mother's blood stream, as will be explained below. After circulation through its terminal capillary vessels the blood flows back again through the veins of the umbilical cord to the infant's body, where it delivers its burden of nutritive substances gathered while passing through the placenta.

Such an arrangement of thin walled blood vessels beneath a protective wall of cells or a sheet of protoplasmic substance is, so to say, standard in the body. It is a practical way to get the blood close enough to other materials to permit exchanges, without letting it escape. A steam radiator retains the steam and yet lets out the heat, by a somewhat analogous arrangement. We see such systems in many places where something is to be taken out of the blood or put into it in the kidney, in all sorts of glands, in the joints, in the chambers of the brain and the eye, wherever fluids must be transferred between blood and tissues or spaces, with or without a burden of dissolved chemical substances. In this kind of a set up the thinner-than paper tubular walls of the capillaries and the relatively thin cellular covering of the villi serve as *semipermeable membranes*, that is to say, strainers so fine that solid particles, even those too small to be seen under the microscope, cannot pass them, whereas fluids and completely dissolved substances of small molecu-

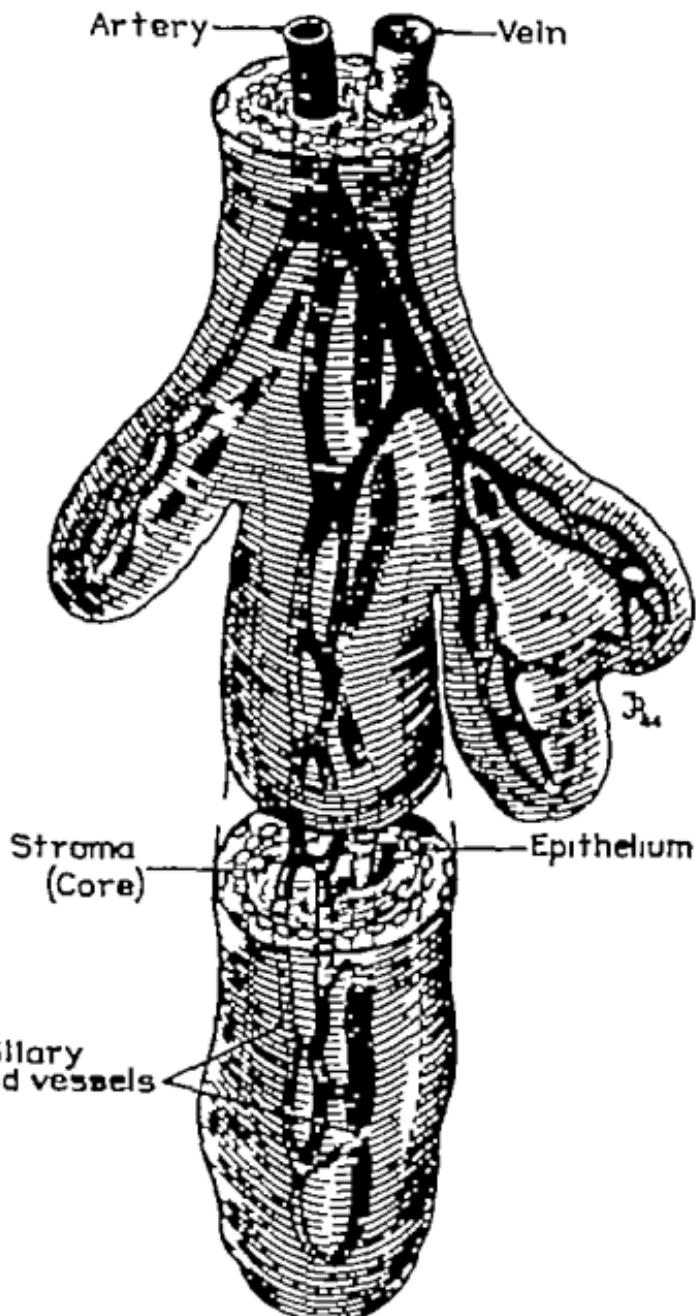


FIG. 10. Part of a fully formed villus of the human placenta, showing course of the blood vessels and arrangement of epithelial covering. It is to be understood that each villus is surrounded by maternal blood which seeps through the root system formed by the villi. Magnified about 160 diameters.

lar size filter through them with ease, from and into the maternal blood pool in which the villi ramify

The semipermeable membrane is nature's commonest device for maintaining the chemical functions of living organisms. The roots and leaves of every green plant on earth are built on this principle. The animal lung is a complex semipermeable membrane system which permits the passage of gases (oxygen and CO₂) while excluding dust and retaining all the ingredients of the blood. Indeed, the surface of every cell is such a membrane, and we have reason to think that even within the cell the wall of the nucleus and the surfaces of tiny inclusions such as fat droplets and enzyme granules are also minute filter zones of the same sort, guarding the very droplets against the entry of irrelevant materials.

I find by teaching medical students that the concept of the semipermeable membrane, simple as it really is, is for some reason difficult to assimilate. I cite therefore a crude but genuine example: the casing of your breakfast sausage is nowadays generally made of cellophane-like material which is semipermeable. It looks as continuous as glass but on a very fine scale, much finer even than the microscope can see, it is a lattice of almost inconceivably small cellulose fibers with inconceivably small slots between them. For medical students I used to demonstrate this fact by putting some exceedingly fine carbon particles into a bag of sausage casing and hanging it in a beaker of water before the class I employed, to be exact, Higgins Indelible American India Ink. The grains of this jet black fluid, some of them scarcely visible under the microscope, will pass an ordinary paper filter with ease, but they are completely retained by the cellophane-like sausage skin and my little black bag of India ink used to hang all afternoon in water which remained perfectly clear. Table salt mixed with the ink, however, passed readily out through the membrane into the water, and could

be tasted there or revealed by chemical tests. Thus a stream of blood, running through such a tube of cellophane or through a thin walled blood vessel, is subject to a filtering action by which gases, salts, and other substances of small molecular size are filtered out through the walls of the tube, whereas the blood cells and also the larger molecules (of proteins, for instance) are retained within the vessel.

The question of permeability, to put it briefly, is a matter of relative size of the particles of matter with respect to the mesh of the strainer. A barnyard fence is impermeable with respect to horses but permeable to mice. The placenta, as we shall see, is impermeable to large molecules but permeable to small ones.

It must be added that when we are dealing with exceptionally fine ultramicroscopic interstices or meshes, as in the semipermeable membranes of living things, certain physical forces come into play which do not operate significantly in everyday straining processes, e.g., the attraction and repulsion of electrical charges on the particles and on the filter itself, these bring about results somewhat different from the workings of the kitchen colander or even of ordinary paper filters of the laboratory type. Any particle that is small enough will pass the kitchen strainer, and a brass strainer will work just like a tin one if the mesh is the same but semipermeable membranes like those of the lung, kidney, and placenta are to a considerable extent selective, permitting the passage of one substance and not another, by reason of their respective chemical and physical properties as well as of mere size. One more reservation should be made, namely that such a semipermeable system as the placenta is in all probability not simply a mechanical filter, even allowing for these small-scale effects for the covering layer of the villi is living substance and quite possibly is able to act upon the substances which pass through it, partially digesting them or otherwise altering their chemical

and physical nature. In this way it may itself perhaps make some substances needed by the infant more readily filterable.

It is possible, though difficult and expensive, to investigate, to some extent, the properties of the placental barrier. The blood in the umbilical cord of a new born baby can be analyzed and compared with a sample taken from its mother's arm vein and thus a good many deductions can be made as to what gets across the placenta. In animals, intensive studies, subject only to the limitations of our knowledge and present methods, can be made by feeding or injecting test substances into the mother or even injecting them under anaesthesia into the fetuses *in utero*, thereafter analyzing the blood and tissues on the opposite side of the barrier.

We know, to begin with, that the placenta does not normally permit transfer of the mother's red blood cells into the embryonic blood vessels, nor of those of the embryo into the mother, even though these red blood cells are only .007 millimeter (.0003 inch) in diameter. It will moreover not even pass substances which are completely soluble, in the usual sense, in the blood plasma if their molecules are of very large size. To be specific, the proteins of large molecular structure do not enter the embryo as such. They must be broken up chemically into components of smaller molecular size, either simpler proteins, proteoses, or the still smaller amino acids. The embryo has to build its more elaborate proteins again from these transferable ingredients. Fats, presumably because they are not soluble in water do not pass the placenta as such. Apparently the body has ways of splitting them chemically and combining them with other substances so that they can traverse the barrier, after which the embryo again revises the combination and rebuilds its own fats. Carbohydrates, which reach the placenta as sugars, are easily soluble in the blood stream and pass the placenta freely, providing a ready supply of

energy for growth. Common salt also passes freely, as would be expected from its properties, and the same is true of the calcium which is so necessary for growth of bone. Foreign salts given experimentally are treated selectively—some are passed and some are not. At least some of the vitamins get through. Some of the potentially harmful albuminous substances against which the body develops "immune reactions" (for example, diphtheria toxin) undoubtedly pass through the placenta. In this fact we have the basis of a very disquieting recent discovery about a disease of the unborn infant (*fetal erythroblastosis*) which we shall have occasion to discuss in Chapter II, §7. Disease germs in general do not get through unless they damage the placenta and so make it leaky.

A very ingenious method of studying placental transmission, already useful, and full of promise for the future, has been introduced in recent years by my colleague Louis B. Flexner. This involves the use of radioactive chemical elements, prepared from ordinary substances by bombarding them in a cyclotron. Salt (sodium chloride) made from radioactive sodium behaves physiologically exactly like ordinary salt, going everywhere in the body in the usual way. It can be detected at once, however, by the use of a Geiger counter or other sensitive electroscopic device, and thus it can be followed wherever it goes. Flexner and his fellow workers Pohl and Gellhorn have found, for example, that sodium chloride injected into the veins of a pregnant guinea pig begins to pass the placenta at once and is evenly distributed on both sides of the barrier, i.e., in the blood of mother and of infant, in a few hours. At present this method can be used only with relatively simple compounds, but after the war, when the chemists have time to put radioactive elements into more elaborate compounds, perhaps even carbohydrates, fats, and proteins, we may expect a

rapid advance in our knowledge of embryonic and fetal nutrition

In summary, then, and subject only to certain technical reservations, nothing gets through the placenta from mother to child unless it is capable of being carried in solution by the blood, and of passing through the walls of the villi and of their blood capillaries, which together constitute an exceedingly fine-meshed semipermeable membrane. There is no other means of communication between mother and child. In particular it should be emphasized in capital letters that there is no connection between their nervous systems. Not a single nerve fiber crosses the placental barrier; there is no channel for the transmission of feelings or intentions, moods, memories, or ideas. The infant is in fact completely shut off from its own mother save for the exchange of simple chemical nutrients and wastes through a screen so fine that it will pass nothing but the smaller molecules of matter.

9

In this regard the proved facts of the laboratory are in flat contradiction to one of the oldest beliefs of mankind. If a mother is discontented or disquieted says Robert Burton in *The Anatomy of Melancholy* "or if by any casualty she be affrighted and terrified by some fearful object heard or seen, she endangers her child. For the strange imagination of a woman works effectually upon her infant, that as Baptista Porta proves, she leaves a mark upon it. In such as prodigiously long for such and such meats, the child will love those meats, and be addicted to like humours."

If a great belled woman see a hare, her child will often have a hare-lip. One Thomas Nickell born in the city of Brandenburg 1551 went reeling and staggering all the days of his life as if he would fall to the ground because

his mother being great with child saw a drunken man reel ing in the street. I saw at Wittenberg, in Germany, a citizen that looked like a carcass. I asked him the cause, he replied, 'His mother, when she bore him in her womb, saw a carcass by chance, and was so affrighted with it, that *ex eo foetus et assimilatus* from a ghastly impression the child was like it.'

To Burton's catalogue of horrors one could go on all day adding others, gathered from hearsay in this present cen tury, and from every level of society. A public lecture in which this theme is discussed never ends without people coming up afterward to take private issue with the speaker, and to add a few more examples from experience in their own family circle. These good people are willing to believe anything a scientist says until he tells them that a mother's impressions cannot reach the infant in the uterus. They know better than that!

It seems to be admitted nowadays that fairly strong pressure is required to force a mental impression across the placenta to the detriment of the unsuspecting infant. Most of the stories involve serious alarm or injury to the mother, or a very strong craving for some peculiar food, or a badly disordered imagination. In the most famous case of mater nal impression on record, however, and the one most hal lowed by time and authority, that of the Patriarch Jacob's goats and sheep in Padan Aran (Genesis 30), the causal factor was nothing more than an unfamiliar sight, of peeled saplings placed by crafty Jacob before the watering troughs and the result was only that the lambs and kids were born "ringstraked, spotted, and speckled," a condition which did them no harm and greatly enriched Jacob. The passage of ideas or visual images across the placental bar rier ought rightly to work with strongly agreeable impres sions as well as with terror, grief, or uncontrollable desire, and in fact many kindly people have suggested using ma

ternal impressions for the advantage of the infant. The young mother is urged to surround herself with peace and beautiful things and to indulge in none but worthy reflections pending the birth of her child. This is good advice, for other reasons. The child will be fortunate, after birth, to have such a mother but beforehand, in sober truth, sweet thoughts are no more soluble in the maternal blood plasma nor any more able to pass a semipermeable membrane of living protoplasm, than are sour moods or tragic emotions. The little half formed brain, thank Heaven, is far beyond the call of our dizzy world of excitement and anxiety. If it were not so, would not the horrors of these years of war be followed in every land by a horror of deformed and wretched babes, offspring of a world of terrorized women?

But this is a matter for more than rhetoric. Even today the timeless superstition goes on, giving the old wives something to gossip about and frightening young matrons who ought to be left in peace. Sometimes it goes to incredible lengths. I know of a case in one of our States only a dozen years ago which cannot be told here in full because the participants are living, in which a young woman of a privileged family suffered an accident during her first pregnancy and had a leg amputated. A combined force of grandmothers and other well wishers insisted that the baby would surely be marked in some dreadful way, and they wrought upon the feelings of all concerned with such success that two doctors (I wonder who taught embryology where they studied medicine?) performed an abortion in the fifth or sixth month adding to the burdens of the unhappy bride another surgical risk and the grief of losing her firstling.

People never remember to tell of Mrs. A., who was nearly frightened to death by a thunderbolt and yet had a beautiful baby nor of Mrs. McB., who would eat nothing but lobsters during her pregnancies but bore one flawless bairn after another, whereas poor Mrs. O C. in the next block,

who couldn't afford lobster, had a baby with a claw anyhow. The scientists may criticize, as they please, the one-sided credulity of the maternal-impressionists, and lecture to their hearts' content about the placenta with its ultra fine filter system and its total lack of nerve connections. They may explain away some cases as pure coincidence and others as the result of inheritance. They may plausibly ascribe the spotted lambs of Father Jacob to the recessive genes of Father Gregor Mendel, A.D. 1866. But they will not be heeded. The eternal process of motherhood, so marvelous and mystical, must carry forever, it seems, not only its blessings of hope and love but also the burden of an ancient fear. There will always be ladies to come up at the end of the lecture to tell about Great Aunt Jane — she had a craving for strawberries, and of course the baby had a strawberry mark. And as an honest man of science, I have to admit, in conclusion, that I myself know of one remarkable case. A woman of my acquaintance had a craving to read *David Copperfield* while she was expecting, and, upon my word, that child was full of the Dickens.

10

I have already remarked that the placentas of the various mammals exhibit extraordinary differences. This has long been known and attempts have been made to classify animals according to the general form of their placentation. All the great apes have disc-shaped placentas, but many monkeys have two discs, on opposite sides of the chorionic sac (Fig. 11). The umbilical cord is attached to one disc, and the second is connected to the first by blood vessels that run on the inner wall of the chorion. In many carnivores the placental tissue makes a girdle around the chorionic sac, forming the zonary type of placenta. This is the case in the dog and cat; in some other carnivores the girdle is open at one place like an unclasped belt, or is interrupted at several

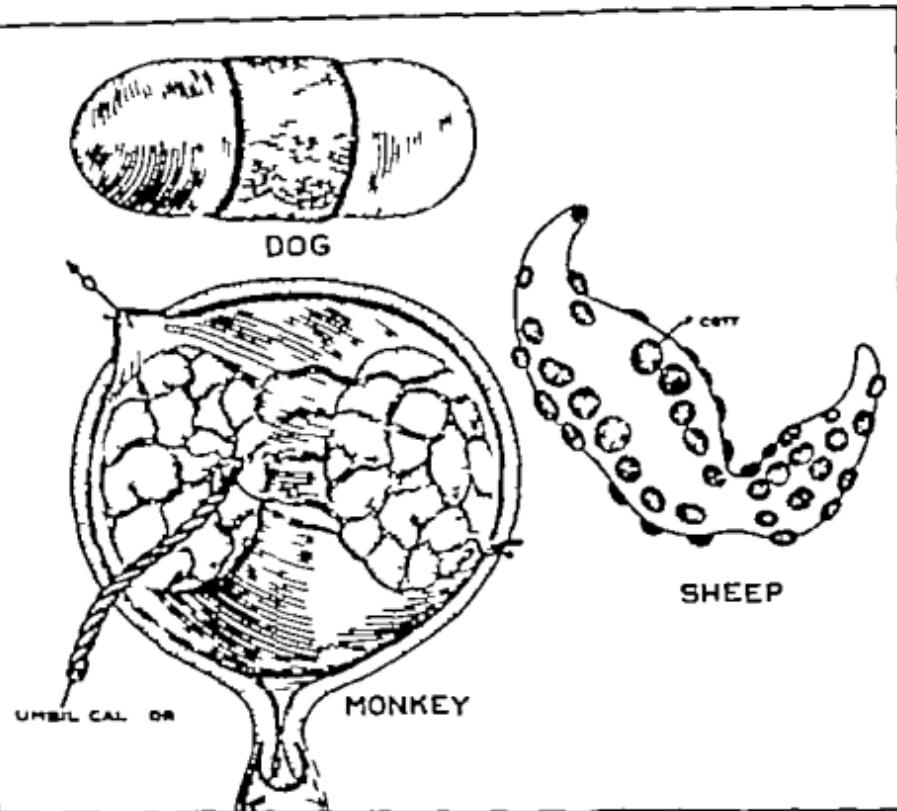


FIG. 11. Various forms of the placenta. The sunray type (dog) and cotyledonary type (sheep) are from diagrams by H. W. Moosman. The intact chorions are seen from the outside after removal from the uterus. F. coty., fetal cotyledon. The monkey's doubly discoid placenta is represented in position in the uterus, the uterus and chorion having been opened, so that the placental discs are seen from inside. For a picture of the singly discoid form of placenta, see Plate VII C.

points. Every cattle breeder knows the cotyledonary type of placenta characteristic of the cow and sheep, which consists of two dozen or more separate placental areas distributed over the chorion, with a simple nonplacental smooth chorionic surface between. In the pig, horse, and deer the placenta is diffuse—that is to say, the whole chorion, or most of it, comes into close contact with the uterine lining, so that transfer of nutrients takes place over the whole area.

There are differences also in the way in which the chorionic tissue interlocks with the underlying uterus. Man and the great apes have completely villous placentas, such as I have already described, in which the tissue that interlocks with the mother's tissue is a system of branching roots. Many carnivores and a good many other animals have, instead, a placental labyrinth constructed like the paper bells sold at Christmas time, which are made of honey combed paper meshes (Fig. 18, B). In such placentas the interlacing leaflets penetrate the uterine lining as do the root like villi of the human placenta. There is a simpler type, occurring in the cotyledonary placentas of cow and sheep, in which multiple folds or pleats of the chorionic surface fit between similar folds of the uterus. A still simpler plan is that of the completely diffuse type, as seen in the pig (Fig. 18, A) in which the chorion is a membrane without folds, labyrinth, or villi, and is merely apposed to the lining of the uterus, as one bag might be inflated inside another, with a minimum of folding and no interpenetration or destruction of maternal tissue.

Finally, there are extreme differences in the finer microscopic structure. In the simplest diffuse placentas like that just mentioned, the surface (epithelial) cells of the chorion lie against the epithelial cells of the internal surface of the uterus (Fig. 12, A, *epitheliochorial*). Whatever chemical substances pass from maternal to fetal blood vessels must pass through the thin cells of the maternal vessel wall (maternal endothelium), the connective tissue, the surface cells (epithelium) of the uterus, the surface cells of the chorion, and the fetal vessel wall (fetal endothelium). In the interfolded cotyledons of the cow, sheep, goat, and their kin, the maternal epithelium is eroded away and disappears in many places, so that there is one less layer involved in the filter zone, as shown in the figure of the *syndesmochorial* type. In the labyrinthine placentas of the cat and dog, the

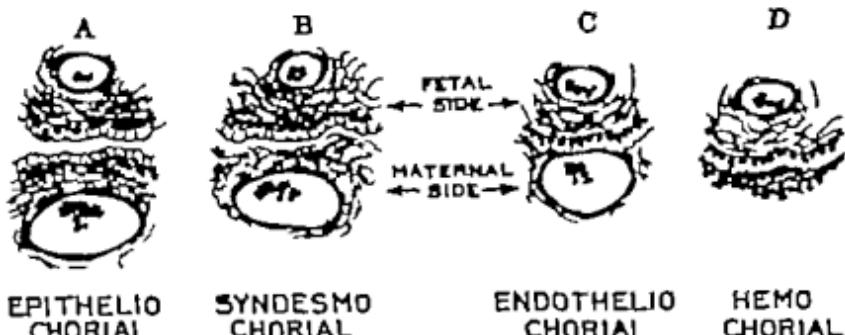


FIG. 12. Diagrams of the cell structure of placentas of the various types as indicated, showing the differing layers of maternal tissue between the maternal and the fetal blood streams. The blood vessels are shown as round open cross sections containing clumps of small round blood cells. Greatly magnified.

This diagram will be understandable if the reader will note that A, epitheliocchorial type, represents a magnified view of the contact between chorion and uterus of the pig, as indicated by a rectangle in Fig. 18, A; that C, endotheliocchorial type, represents part of a strand of the labyrinth shown in Fig. 18, B; and that D hemochorial type, represents a bit of the wall of the villus shown in Fig. 10. In the latter there are no maternal cells at all between the maternal blood and the fetal epithelium. From *American Journal of Obstetrics and Gynecology* by courtesy of C. V. Mosby Company St. Louis, and of Louis B. Fleisher and Alfred Gelhorn.

chorionic labyrinth destroys not only the maternal surface cells but most of the connective tissue as well, leaving only the naked maternal blood vessel walls (endothelium) between the vanes of the labyrinth (Fig. 12, C, *endotheliocchorial*). As already described, in man and in other Anthropoidea all maternal structures in the path of the invading villi are broken down, even the blood vessels, and the villi hang directly into the maternal blood pool. In Fig. 12, D, *hemochorial*, we see how the maternal blood directly bathes the chorionic epithelium, leaving only the three fetal tissue layers between maternal and fetal blood. In some other animals (e.g., the rabbit) investigators have found a further development of this fourth stage here even the surface cells of the labyrinthine chorion may go in places, leaving nothing but a little connective tissue and the endothelium of the

fetal blood capillaries as a partition between the blood stream of the embryo and the blood pool of the mother

Flexner, Gellhorn, and Pohl measured, by the use of radioactive sodium salt (chloride), the transfer of sodium from mother to fetus in species having all these various types of placenta. They discovered the remarkable fact that the amount thus transferred across a unit weight of placenta in a unit of time, at a comparable stage of late pregnancy, varies according to the structure of the placenta. In those with all six cell layers the rate of transfer is much less than in those with fewer. The relative figures, expressed as the amount of sodium in milligrams passing a given weight of placenta in one hour, are sow (epitheliochorial), .026 goat (syndesmochorial), .41 cat (endotheliochorial), .69 guinea pig, 6.1, rabbit, 6.8, rat (hemochorial), 8.8. There is, of course, no such difference between these species in respect to other physicochemically determined functions like body temperature, pulse rate, and basal metabolism but the fact is that among mammals everything that has to do with reproduction is more variable than other bodily systems.

When we consider the total variation of structure made possible by permutations and combinations of the gross form, the different types of interlocking from diffuse to labyrinthine and villous, and the four or five degrees of difference with respect to the cellular layers, it is easy to see how the study of the placenta has become a special branch of microscopic anatomy. No two animals have placentas exactly alike. Experts like Grosser of Prague and Wislocki of Harvard, given well prepared slides of placentas of the various species for microscopic examination, can name any species, if they have seen it before, after a few minutes' examination but only such an expert could distinguish the placenta of the gorilla from that of the human.

Naturally such close resemblance between certain spe-

cies, taken in conjunction with the wide range of general variation, confers upon the placenta very great interest for students of evolution and of the relationships of the mammals to one another. It was long ago found that the gross forms (diffuse, discoidal, zonary, cotyledonary) are so scattered through the mammals as to give us no clear guide to their possible line of descent. The existence of the four gradations of contiguity as seen under the microscope, pointed out by Grosser as described above, suggested at once that these form a progressive series from the epitheliochorial type, in which the uterine surface is intact, on to the hemochorial type, in which the greatest invasive destruction of maternal tissue takes place, with the thinnest barrier between maternal and fetal blood and the highest rate of transfer. It was easy to suppose this was the sequence of evolution. The blastocyst of the primitive mammal, it might be thought, settled against the maternal surface and thus at once formed a contact of chorion to maternal epithelium that is to say, an epitheliochorial placenta. It was supposed that at a later stage the erosion and the ingrowth of villi or labyrinth began progressing until in certain advanced species all the maternal elements were destroyed and the hemochorial stage was reached. Since the human placenta is hemochorial, this conjecture suits our natural tendency to place our own species high in the scale of evolution. Conversely, and perplexingly, it places at the "low" or primitive end of the series certain species which we know from other anatomical facts to be highly specialized. The domestic pig has one of the simplest diffuse epitheliochorial placentas (Figs. 18, A, and 19, A) but it is by no means a primitive mammal. Wislocki attacked the problem anew, a few years ago, by listing the placental types of all mammals, so far as known, and plotting them on a diagram of the evolutionary relationships as currently accepted from studies of the comparative anatomy of living and fossil mammals.

Such a diagram of course looks like a tree, a family tree in fact, with the most primitive groups near the trunk and the most advanced and specialized groups out on the branches. The result showed that animals having epitheliochorial placentas are widely scattered among the mammals, tending to occur in animals which are in other respects highly specialized, in other words, they are out on the branches of the family tree. The logical inference, from which there is no obvious escape (although it staggered many biologists at first and is still not acceptable to some) is that the invasive placentas are nearer the primitive type than are the superficial, noninvasive placentas, and that evolution did not begin with a diffuse epitheliochorial placenta like the pig. How it did begin is anybody's guess, since the really primitive mammals are extinct and we shall never see their placentas. Perhaps (and I hasten to say that this is my own way of putting it, not that of the specialists on the subject) the primitive mammalian blastocyst settled down on the epithelium of the primitive uterus, and responded to the contact by forming a trophoblastic thickening something like that of the early monkey embryo (Fig. 5, C). From this beginning, nature may have experimented at once with all sorts of variations such as villous or labyrinthine down growths, reaching diverse degrees of invasiveness and of destruction of the maternal elements. The interstitial or sub-surface nesting of the blastocyst in man and the anthropoid apes would be a further modification. Placental types with a widespread surface contact of chorion to uterine lining without invasion, like that of the pig, may well represent another kind of variation. Thus the noninvasive and the invasive types probably represent parallel developments, not a successive evolution of one from the other.

When the early embryology of all the mammalian forms is more widely explored, we shall probably gain a much better comprehension of this important and tantalizing prob-

lem. At present, as the reader will perceive, we had better be very cautious about setting up any sort of ladder-like scale of evolutionary progress, as far as the placenta is concerned, with our own species at the top of it.

11

Let us now resume consideration of the actual body of the embryo, which when we left it in §5 at the age of about 13 days was still a mere disc of ectoderm cells with underlying endoderm (Fig. 6, E). The successive transformations by which this simple structure is converted into a baby can never be observed without astonishment and awe. They have been studied for centuries with all the ingenuity, artistic skill, optical and mechanical aids at the command of each generation of embryologists. We have therefore a fairly complete description of the changes in form by which the various organs and tissues take origin one by one from earlier-developed tissues and arrange themselves to make up the body. Such a description, pursued to the last detail, is a complicated business. The two great volumes of such a book as the Keibel Mall *Manual of Human Embryology* are not large enough to contain it all. For our present purpose a very brief sketch of embryogenesis must content us; readers who wish more solid information may turn to the article on Embryology in a good encyclopedia, or to one of the excellent textbooks prepared for collegiate and medical students.

Dr G. L. Streeter has arranged a series of pictures of models and of actual embryos from the Carnegie Collection which gives an excellent idea of the external form of the embryo at successive ages. In Plate VIII, A, we are looking down on the back of the embryonic area, the amnion having been cut away around the edges and lifted off. At this age, 18 days, the embryonic area is no longer a disc—it has elongated in one axis and therefore has the form of a

shield with a head end and a tail end, and by consequence a right and a left side. A symbolistic mind might pause at this point to reflect that even before its first three weeks of prenatal life are completed, the embryo finds that there are two sides to human affairs and thus begins to face a lifelong series of choices between the right- and the leftward turn. At the top of picture A is the broad and presently featureless head region, and below it at the middle of the axis is the *primitive knot* followed by the groove-like *primitive streak*. This is a region of growth which moves tailward leaving behind it the structures of the trunk as they are organized. In picture B we see two massive folds, largest at the head, and between them a deep groove. As shown in C and D, the folds coalesce, beginning at the middle and working both ways. Thus they roof over the groove, in this way a tube of ectoderm is buried under the surface from head to tail, forming the brain in the head and the spinal cord in the neck, trunk, and tail.

If the reader will now look back at Fig. 9, A, he will see in diagrammatic fashion how the headward and tailward growth of the embryonic shield draws out the underlying endoderm into a more or less tubular canal having a "head gut" and a "hind gut" but in its middle portion still opening into the yolk sac. The neck of the yolk sac thus ultimately becomes a relatively narrow passage from the em-

DESCRIPTION OF PLATE VII

Three stages of formation of the human placenta and membranes. In A (fourth week) the chorion is everywhere covered by villi, but those on the more superficial, bulging side are beginning to thin out. In B (six weeks) the villi have disappeared from that side, leaving only the basal villi to form the placenta. The amnion is swelling and will ultimately fill the chorioamniotic cavity. In C (five months) the placenta is definitely formed, the amnion has fused with the chorion, and the two membranes (amnion and chorion) have fused with the opposite wall of the uterus, obliterating the uterine cavity. Drawn by the late Max Broedel. From the *American Journal of Obstetrics and Gynecology* by courtesy of C. V. Mosby Company

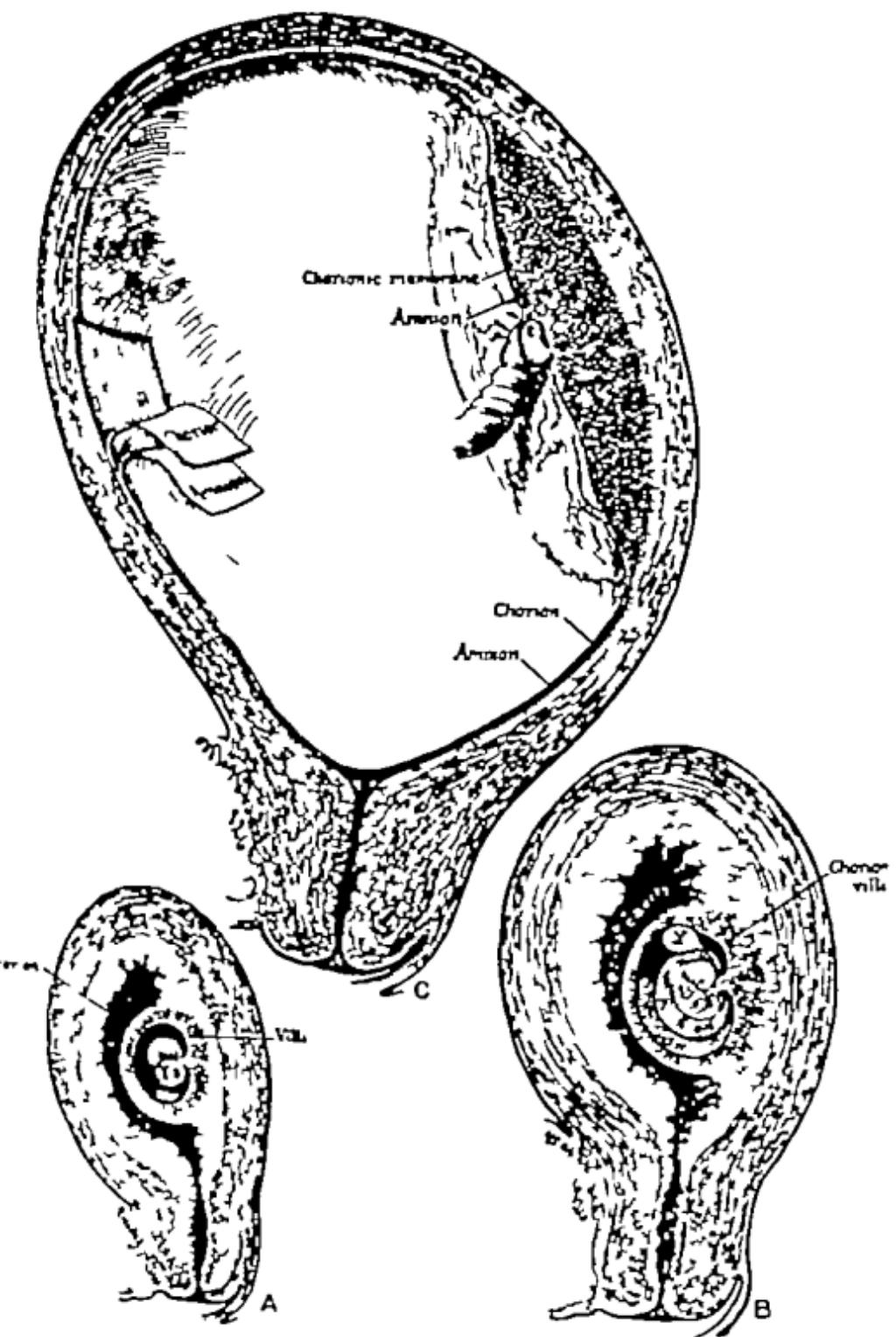
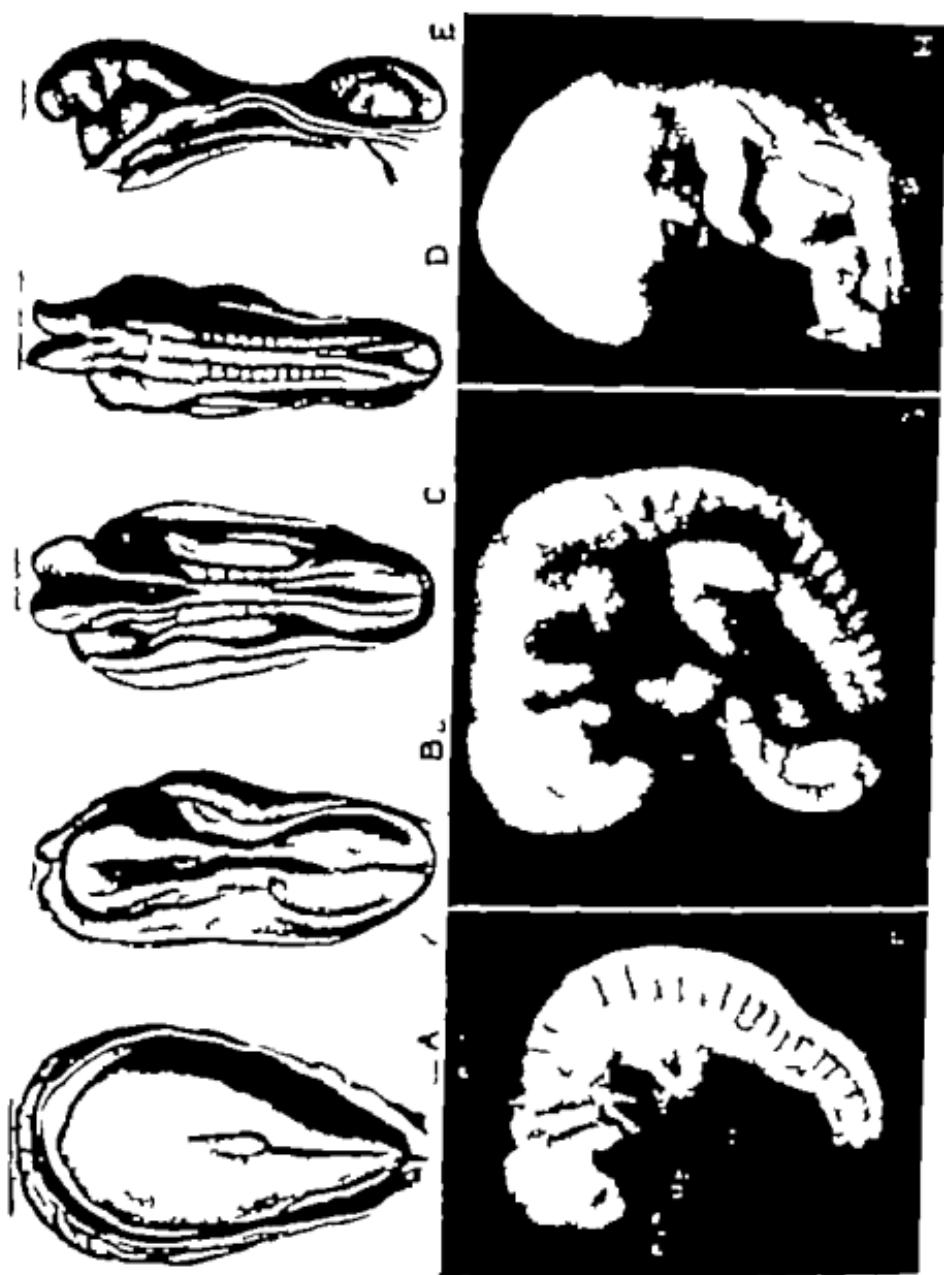


PLATE VII

PLATE VIII



bryo along the umbilical cord. In Plate VIII, E, representing an embryo from which the yolk sac has been cut off, the opening may be seen as a long narrow slit opening into the body of the embryo from the left of the picture.

A cross section of any of these embryos would reveal, between the outer ectoderm and the endoderm, the third tissue or mesoderm. Some of this tissue condenses to form a row of *somites*, small squarish masses of embryonic connective tissue arranged in regular series along the two sides of the spinal cord from the lower part of the head to the tip of the tail. These are clearly seen lined up like a row of beads beneath the ectodermal skin in all the pictures of Plate VIII from C to G inclusive. They give rise to much of the muscular system of the neck and trunk. Traces of this segmental origin persist into a few muscles of the adult body, e.g., the intercostal muscles. The arrangement of the somites also conditions the serial arrangement of the vertebral segments of the bony spinal columns, each of which forms at the level of the division between two successive somites. All the vertebrates from the cartilaginous fishes to man exhibit a series of somites unmistakably similar to those of man and the other mammals. This has been taken to suggest that the common ancestor of the vertebrates must have been a segmented animal of some sort. As the muscles begin to form

DESCRIPTION OF PLATE VIII

Development of the external form of the human embryo, from models and specimens in the Carnegie Collection. A, about 16 days (No. 5960) view of dorsum (back) of germ disc after removal of roof of amniotic cavity x 30. B, about 18 days (No. 1878) x 28. C, about 19 days (No. 4216) x 23. D, about 20 days (No. 8074) x 23. E, about 22 days (No. 5072) x 15.5. F, fourth week (No. 6097). Ph., pharyngeal bars; Ht., heart, x 12. G, fifth week (No. 1330) x 8.5. H, eighth week (No. 6202) x 2.5. Cited magnifications are approximate. Selection and arrangement by G. L. Streeter. In part after publications by C. H. Heuser & W. Ingalls, F. Payne, W. J. Atwell, G. W. Corner. From *Scientific Monthly* by permission.

from the somites, nerve twigs from the lower brain and the spinal cord grow into them, forming the beginnings of the motor nerves.

During the third week the heart is formed by cells of the mesoderm under the head, which organize themselves into a thin walled looped tube. This links up with the blood vessels on the yolk sac and with those which spread throughout the mesoderm of the animal body and via the body stalk to the trophoblast. When the heart begins to beat, it soon causes a circulation of blood through the whole system. The heart, enclosed in its pericardial sac, is seen in Plate VIII, E, as a large mass near the top, to the left of the head, and in the corresponding region of F as a semitransparent sac (Ht.) (see also Fig. 13). In Plate VIII, G, the ventricle of the heart is a white mass just above the tip of the tail.

Pictures E, F, and G of this series clearly show the row of pharyngeal bars (indicated by Ph in F) which have figured often, under the somewhat misleading name of "gill bars," in countless discussions of human evolution. In the human embryo 5 of these ridges develop, separated by 4 grooves, but in our pictures only 3 can be seen. The pharyngeal bars of mammalian embryos appear in the same region of the body as the gill bars of fishes, salamanders, and tadpoles. Each of them carries, moreover, an embryonic artery (aortic arch) which runs from the heart to join the aorta, like the gill arteries of those animals. In the amniotes (reptiles, birds, and mammals), however, the pharyngeal bars never function in respiration. Some fossil reptiles had rudimentary gill filaments upon the bars, but this is never the case in mammalian embryos, nor do the grooves between the bars break through into the pharynx, forming gill clefts, as they do in fishes, in which they permit the passage of water (with oxygen dissolved in it) past the gills. Furthermore, the pharyngeal bars of mammalian embryos begin, as soon as they are formed, to enter into further stages

of growth, contributing ultimately to the organization of the face and jaws, the external ear and the auditory canal, the tongue, thymus and parathyroid glands and other structures in the upper neck. The first two pairs of aortic-arch arteries degenerate and the last three become parts of the great aortic and pulmonary arterial trunks.

The temporary existence of the pharyngeal bars has frequently been used in support of the theory of embryonic recapitulation, which in its now-obsolete extreme formula tion sets up an ascending scale of animals—namely fish, amphibians, reptiles, mammals—and states that the embryos of the higher forms pass through stages resembling the adults of lower forms. On this theory the pharyngeal bars, for example, are said to reproduce or recapitulate a fish stage in our evolution. Actually, however, they are not gills, as we have seen, but rather a structural groundwork occurring in the embryos of fishes, amphibians, reptiles, and mammals, which in fishes and amphibians is used as a basis upon which to build mandibles and gills, and in reptiles, birds, and mammals to make jaws and neck-organs but not gills. What we may safely deduce from the similarity of this arrangement in all classes of vertebrates is that they inherit their pattern of growth through some one common protovertebrate ancestor, of fish like general character though not exactly like any present-day fish, which had a series of arterial loops lying in a set of bars in the walls of the pharynx. It may be added, as a plausible guess, that the system served to take oxygen from the water. The descendants, as they evolved into the various classes, necessarily inherited such a pattern, but they worked it over into new forms suitable for their needs. To say that the pharyngeal bars suggest a common origin for fish and man is a very different thing from claiming that as embryos we humans have gills and therefore we must have had a fish for a direct ancestor.

A trained embryologist can see the earliest rudiments of the eye and the auditory apparatus at a stage like that of Plate VIII, C. At a slightly later stage these organs can be clearly descried by anyone, as indicated in the picture F. The object labeled *ear* is the ear vesicle, which is to sink inward and become the internal ear, the external ear is formed from the first and second pharyngeal bars.

The limb-buds are seen in the fifth week, the arm appearing before the leg. Both are shown in picture G. This figure shows too that the human embryo possesses a tail, as evidence (final evidence, if the pun be permitted) that man is a vertebrate and has inherited the common patterns of that ilk. It is really only a tail rudiment, however, for it rarely gets bigger than the end of a pin and cannot be considered a real waggleable tail any more than the pharyngeal arches are real gills. It is only the bud, the *Anlage* as the German embryologists say, from which nature could have built a full fledged tail like that of the monkeys. Unlike the pharyngeal bars, however, the tail is not built into something else. By the fifth week it is already being outgrown, and within two weeks more the development of the rump has so far exceeded that of the tail that the latter becomes buried and persists only as the little terminal part of the spinal column, the coccyx.

The head end of the digestive-respiratory tract ("fore-gut") breaks through the ectoderm to form the mouth, and the "hind gut" likewise breaks through at the anus (Fig. 13). Whole chapters could be written about the development of the digestive system and its outgrowths, including the salivary glands, the liver, the pancreas, and the lungs. I shall not even touch upon these, nor upon the development of the great connective structures, bones, muscles, tendons, blood, and lymph, nor of the reproductive system and the organs of internal secretion, all of which are well described in the textbooks.

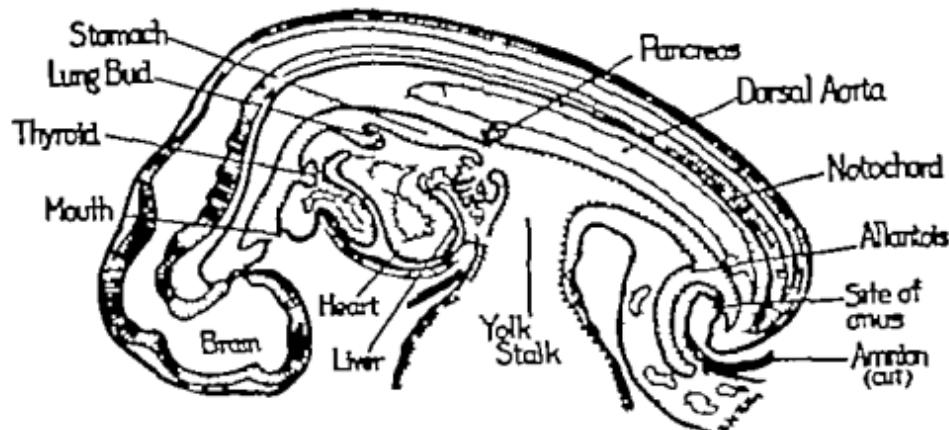


FIG. 18. Schematic and partly conventionalized diagram of human embryo at end of first month, showing position of brain, heart, yolk sac, and digestive tract. Greatly magnified. Drawn by Bradley M. Patten. From his forthcoming *Human Embryology* by courtesy of the Blakiston Company

By the eighth week (see picture H of Plate VIII) the embryo, or fetus as we now call it, is an unmistakable human being, even though it is still only three-fourths of an inch long. The obviously transitory structures which give the embryo its unfamiliar, nonhuman appearance, such as the pharyngeal bars, the somites, the external position of the heart, are now gone or covered up or converted into something more familiar. The fetus is clearly a vertebrate with four limbs; the shell-like ear hints that it is an ape or something of that sort; the disappearance of the tail rudiment confers a certain dignity upon the silhouette, ranking the creature as at least one of the higher Anthropoidea; the trivial nose and flat face say it is human, and the great bulge of the brain predicts that this being is destined to feel, think, and strive beyond all other species that live on earth.

This we can see in pictures—but if we could only observe such an incipient human being in its proper environment, nested within the uterus, we should also see the vividness of life—muscles already able to contract, limbs that move if they are touched, a heart that beats and keeps the blood

flowing throughout the body and through the pulsating arteries of the umbilical cord to and from the placenta. Within this microcosm the organs and tissues are teeming with the processes of growth, the cells multiplying, the parts enlarging and shifting each toward its appointed place and task. This is not only preparation for life it is life itself.

Thus to the seeing eye the human embryo from egg to birth is an archive in which is written the evidence of its descent as an animal, a vertebrate, an amniote, a mammal, a primate and it is an organic germ, in which the gift of life is intrinsically bound up with the necessity of growth and of ineluctable change.

II

PRENATAL FATE AND FORE ORDINATION

The voice said, Cry And he said, What shall I cry? All flesh is grass, and all the goodness thereof is as the flower of the field: The grass withereth, the flower fadeth; because the spirit of the Lord bloweth upon it: surely the people is grass.

1

IT is with hesitation that I begin this chapter of a book which aims to be coolly scientific with the narrative of a personal experience that broke upon my steady toil some days as a medical student with the suddenness of an apocalyptic vision. The reason for telling it here is that it will explain the inclusion of a chapter on prenatal mortality, and justify my own persistent interest in the subject ever since the time I helped to fight the Devil for the soul of an infant, beneath the cross of St. Agnes. If it seems incongruous that the tale begins in the very forecourt of Heaven and then descends to bare facts discovered by a mundane and even heretical young scientist, in a hog butcher's establishment on the West Side of New York, that is merely the way of our science of embryology, which comes so close to the daily life of mankind that it leads its students into unexpected situations.

When I was a medical student of the third year, for reasons of no present concern I secured permission to absent myself one day each week from the academic clinics and to spend that time at work in a hospital which happened to be of the Roman Catholic Church. My tasks were those usual to a junior intern. I interviewed patients, made laboratory tests and passed instruments in the operating room. There,

one day, when the morning's work was over and we were about to put away the instruments, we were abruptly called back by the admission of an emergency case. Our patient was a young woman, eight months pregnant, and healthy a few hours before, who had suddenly suffered the rare internal accident of premature separation of the placenta. The disastrous collapse thus produced had brought her near to death. Emergency measures instantly begun by the resident surgeon were too late, and it became evident that she was expiring. To me, the youngest person present, and ignorant of Catholic beliefs, the tragedy of this moment was tinged with wonder at the ensuing scene. The chief Sister of the operating room, swathed as she was in sterile gown, cap, and mask, assumed a kind of spiritual command over the young surgeons, after a whispered word from her they began to count the last pulsations of the patient's heart. When the count slowed and ceased, the resident surgeon with urgent rapidity performed a Caesarian section and in no more time than this sentence takes in the reading the motherless infant was brought limp and breathless into the world. At once, before any effort was made to revive it, the Sister stepped forward and took up a flask of salt solution, now converted by some miracle of faith into holy water. As she uttered, amid our perfect silence, the solemn formula of baptism, I for one half expected to hear the rush of angels' wings and to see the glitter of heavenly hosts, come to join us in this battle for a Christian soul. But the rite was in vain—the child too was dead, and dying thus in original sin was excluded forever from the sight of God, though not (if St. Thomas Aquinas be right) from the privilege of rejoicing, outside Paradise, in His mercy and love.

8

The infant whose brief story I have just told reached the eighth month of prenatal life before it was overtaken by

disaster. Many another embryonic life is interrupted in a less spectacular way, at an earlier stage of gestation. The rate of prenatal mortality is much higher than is generally known; there is good reason to suppose that at least one-third of all the ova that are fertilized fail to survive to full term. As a result of causes which are to be discussed in the following pages, interruption of growth and cessation of life may occur at any stage, beginning with the earliest which we can recognize under the microscope. The Carnegie Collection contains several abnormal human embryos younger than sixteen days.¹

Abnormality occurring in utero takes various forms. The embryo or fetus may simply cease to thrive, the blood circulation stops, the tissues break down, and the products of conception are discharged from the uterus as a miscarriage. In animals such embryos and even good-sized fetuses are frequently resorbed—that is to say, their tissues disintegrate completely and are received back into the maternal blood stream—but the human uterus is quite intolerant of moribund material and seldom retains a dead embryo or fetus. Again, abnormality may result in the production of local deformities, or reduplication of limbs, or other bodily peculiarities in various degrees, the result being called a monster from the Latin word *monstrum*—a portent or marvel. Sometimes infants thus affected are able to survive and to be born, sometimes the defect is incompatible with life. It is quite clear now to embryologists that embryonic defects run the whole gamut from total breakdown and abortion to outright monstrosity, with all sorts of intermediate conditions. It is also now clear that all these defects, whether

1. An expectant mother who happens to read this chapter need not be alarmed. A large proportion of the cases included in the above calculation occur so early that they are not recognized as pregnancies. Once the implantation is well established and the pregnancy recognized, the probabilities are greatly in favor of a normal outcome.

they involve serious deformity or are very slight, are produced by the same set of causes but this was not always obvious, and the thought of the lay public, as well as of scientifically minded doctors of past times, as to the causes of prenatal abnormality, concerned itself largely with monstrosities. Naturally the more outspoken deformities—"Siamese" twinning, for instance, or lack of an important bodily part—attracted greater attention than the mere abortion of a small embryo. The latter could be passed over as a mishap, the former awoke superstitions and set up fears, until even the physicians were inclined to ascribe many of these unfortunate births to supernatural or psychological causes.

I cite here a tabulation of the causes of monstrosity, extracted from a long passage in *The Workes of that Famous Chirurgeon Ambroise Parey*.² It is worth a careful reading, because it sums up the ideas of past ages. Later in this chapter I shall give another such list, as of 1944; the differences in outlook will illustrate the very point that the founder of the Terry Lectures wished to establish, that science can indeed contribute to the broadening and purification of religion.

"There are reckoned up many causes of monsters, the first whereof is the glory of God, that his immense power may be manifested to those which are ignorant of it. Another cause is, that God may punish men's wickednesse, or show signs of punishment at hand. The third cause is, an abundance of seed and overflowing matter. If, on the contrary, the seed be anything deficient in quantity, some or more members will be wanting, or more short and decrepitate. The ancients have marked other causes of the generation of monsters—the force of imagination hath much power over the infant. Monsters are bred

². Translated from the French by T. Johnston (1634 ed.).

and caused by the straightnesse of the womb by the ill placing of the mother in sitting, lying downe or any other site of the body in the time of her being with child By the injury of hereditary diseases, infants grow monstrous, for crooke-backt produce crooke-backt, lame produce lame, flat nosed their like. Monsters are occasioned by the craft and subtlety of the Devill "

To summarize these causes

- 1 The will and act of God,
- 2 Overabundance or defect of the seed,
- 3 Power of the mother's imagination (maternal impressions),
- 4 Narrowness or malposition of the uterus,
- 5 Physical injury to the mother,
- 6 Inheritance of deformity or disease,
- 7 The craft and subtlety of the Devil and his agents
(i.e., witches and magicians)

Paré was a man of originality and insight, but the problem of the causes of fetal abnormality was too complex for solution in the current state of knowledge. The reader will have noticed that his conjectures, which sum up the ideas of ages past, fall into two classes, on one hand the supernatural and magical and on the other mechanical explanations involving only crude forces within the range of everyday experience. Without the microscope, without knowledge of the circulation of the blood, a fetus could only be understood as something that grows in the uterus as a flower grows in a flowerpot indeed the material causes of abnormality suggested by Paré could equally well have been put forward by an uneducated 16th-century gardener to explain a sickly or deformed plant namely, excess or insufficiency of the seed narrowness of the womb, as of the flowerpot malposition as when the mother lies too long on one side or a flowerpot lies overturned in the garden and

actual direct injury. The only item in his list of causes of monstrosity that is not either supernatural or crudely mechanical is that of heredity—"crooke-backt produce crooke-backt"—but such an inheritance of gross deformities was also within the purview of the gardener, and in Paré's time could not be accounted for by any material explanation.

From his speculative classification of causes we can see why the pathology of the embryo had to wait until the 20th century before a really helpful analysis of its problems could be made. In the first place, the actual cases were often so astonishing and so distressing that it seemed necessary and sufficient to ascribe them to acts of God or the Devil. In the second place, it was impossible, for lack of knowledge of normal early embryology, to recognize the abnormal embryos at an early enough stage to understand the real nature of the defects. In the third place, the physical causes of disease of the fetus, as of disease in general, could not then be traced beyond the limits of naked-eye observation into the realm of the microscopic cells, where better understanding lies. The development of scientific teratology (as the study of abnormalities of the embryo and fetus is called) necessarily depended upon advances in general biology and medicine, and particularly upon progress in normal embryology.

Beginning shortly after the time of Paré the first of a long succession of very able men began to study the development of mammals and birds. Jerome Fabricius of Acquapendente (1533–1619) revived at Padua the study of the hen's egg at successive stages of incubation, almost forgotten as a scientific method since the days of ancient Greek biology. He was also the first to explain and depict with thorough understanding the placenta and the fetal membranes of mammals. His pictures of the cotyledonary placentas of sheep and cow, and of the amnion, chorion,

actual direct injury. The only item in his list of causes of monstrosity that is not either supernatural or crudely mechanical is that of heredity—"crooke-backt produce crooke-backt"—but such an inheritance of gross deformities was also within the purview of the gardener, and in Paré's time could not be accounted for by any material explanation.

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and allantois of various mammals could be used today in the classroom. William Harvey, who had been a pupil of Fabricius when a student of medicine at Padua, made prolonged and skillful observations first on the hen's egg and then on the King's deer. He learned how to find the embryos of mammals at relatively early stages and proved that their development is essentially like that of birds. Another great step was taken about 1673 by Marcello Malpighi, who first seriously utilized magnifying lenses in the study of embryos—the clarity and detail of his drawings of the embryonic chick at once instated the microscope as the chief instrument of the embryologist, and gave to his successors in this branch of science the means of seeing and describing the details of embryos too small for observation by the unaided eye. By 1827 (the date of von Baer's discovery of the mammalian egg cell) the general appearance of the mammalian embryo was known at all stages and enough human embryos had been seen, under the lens, to provide knowledge of the external characteristics of our own species from about the sixth week on.

Meanwhile, in the latter half of the 18th century, several distinguished anatomists—namely John Hunter, Albrecht von Haller, and Caspar Friedrich Wolff, had begun to perceive that congenital defects and deformities do not represent wild or random disorder in growth but are modifications of the normal embryonic development. In 1822, when Johann Friedrich Meckel published at Leipzig his *Handbuch der pathologischen Anatomie* devoted in part to the description of malformation and anomalies in prenatal and postnatal life, he was able to discuss the subject without mysticism, on the basis of known embryological facts. He recognized, for example, that certain defects represent merely the persistence of anatomical conditions that are normal at an earlier stage of the embryo, citing such examples as cleft palate and *ectopia cordis* (abnormally super-

ficial position of the heart) He understood that other defects result from local disturbances of growth in embryonic stages, so that a part of the body becomes atrophic or hypertrophic as the case may be. Thus attention was focused upon normal embryology as the basis of an understanding of the abnormal, and teratology became a recognized branch of science, worthy of the attention of serious investigators because it now offered the possibility of analyzing observed cases with reference to an established body of knowledge. The subject did not, however, lose any of its fascination as it became more scientific, and it rapidly acquired an immense literature. The Italian Taruffi published an 8-volume *Storia della Teratologia* between 1881 and 1895, and Schwalbe's *Missbildungen des Menschen und der Thiere* (1906), a standby of the laboratories, is almost as large. All the malformations ever reported have been classified and given suitable technical names according to one authority's system or another's, and as far as possible the deformities, deficiencies, inversions, and reduplications have been explained in terms of the normal structures in which they arise.

3

No amount, however, of description and classification of anomalies in late stages can tell us what caused them. It became increasingly clear that it would be necessary to collect the earliest discoverable specimens of deformed or otherwise pathological embryos, in order to detect the abnormalities in their incipiency. A fairly large number of young pathological embryos were described between 1880 and 1900 by the great Leipzig anatomist Wilhelm His, by Carlo Giacomini, and others in Europe. The most important communication on this subject, however, came from the American Franklin P. Mall, a brilliant graduate of the University of Michigan Medical School, who went to Ger-

many to continue his studies and had the good fortune to spend a year with Wilhelm His. When Mall returned to the United States he began his own collection of embryos, which later he made the nucleus of the Carnegie Collection in Baltimore. From the very first days of his work Mall was as deeply interested in the pathological as in the normal, and by 1908 he had the material for a great monograph, *The Origin of Human Monsters*. At this time he had 434 embryos, of which 163 were pathological. These specimens came to Dr. Mall from hospitals and practicing physicians to whom he had made repeated appeals to send him embryos from miscarriages and operations.

In order to make perfectly clear what Mall deduced from his collection, it must be understood that the abnormal specimens which he studied were by no means monsters in the usual acceptance of the word—that is to say, they were not the spectacular creatures with animal-like visages, or reduplication of limbs, or cyclopean eyes, and so forth that had been the objects of mingled horror, curiosity, and scientific interest for centuries. Most of them were less than eight weeks old, and they were simply embryos that had failed to develop in a normal way. Readers who followed the sketch of normal early development in Chapter I of this book will have no difficulty in understanding how Mall classified them. Some of them, he pointed out, were merely atrophic—that is, undersized and retarded in the development of their tissues—or they were mere remnants of atrophic embryos. There were chorionic sacs containing an amnion but devoid of an actual embryo. In others there was neither amnion nor embryo within the chorion. Others contained embryos in various states of dissociation, with the tissues and organs growing in irregular fashion, so that the embryos represented every grade of change from almost normal to a little nodule of irregular tissue that would not have been recognized as an embryo had it not been found

associated with placental villi and other accessory evidences of pregnancy

Most of these abnormal embryos had become specimens in the laboratory because they were incapable of development beyond a certain point. The circulation of blood had ceased, or had never even begun, and the chorionic tissue, in spite of its strong inherent tendency to grow even under difficulties, had finally succumbed and was expelled. Mall's collection also contained a number of cases of tubal pregnancy, in which the blastocyst had lodged in the Fallopian tube (oviduct) and had developed there until its growth either ruptured the tube or produced severe pain, in either case compelling an operation. In short, these embryos were destined to an early end, and some were already dead, before they came into the hands of the physicians and surgeons who sent them to the embryologists.

These blighted specimens which Mall was so eager to study would thus seem, at first thought, to represent a class of defective embryos quite different from the monstrosities occurring as advanced fetuses or even as living infants, which had attracted so much attention from earlier workers. In past centuries they would have been discarded as completely uninteresting from the standpoint both of teratology and of normal embryology. Some would not even have been recognized as embryos. Mall, however, was struck by the fact that many of his early pathological embryos exhibited certain defects which are also very common in monsters. The clearest instance of this extremely important observation is seen in the defect called *spina bifida*. The reader will recall that the spinal cord of the embryo is formed quite early, beginning in the third week, when the two neural folds take form alongside the main axis of the embryonic shield (see Plate VIII, Figs. B to E). The surface layer (ectoderm) dips down between the folds, forming a groove which is later closed over by the coalescence of the

folds. In this way the neural tube is formed below the skin at the head end it becomes the brain, in the neck and trunk it becomes the spinal cord. One of the commonest of embryonic defects is a failure of the neural tube to close completely, or a reopening after closure, so that at one part or another of its length, and to various degrees of extent, it remains laid open to the outside. The tissue which would normally form the inner layers of the spinal cord is then exposed. In such a case the bony structure of the vertebral column, which subsequently develops from mesoderm around the spinal cord, is prevented from forming its normal closure over the back of the cord. Hence the name *spina bifida*, divided spine. Extreme cases, in which long stretches of the spinal cord and even the base of the brain are open and exposed, are usually associated with other defects and are destined to miscarriage or stillbirth. An infant thus afflicted with multiple defects, which lives long enough in utero to be stillborn near term, or even survives for a while after birth, would be classed as a monster. Spina bifida has therefore long been known as a frequent characteristic of monstrosity. On the other hand there are slight cases of spina bifida in otherwise normal infants, which can be repaired surgically. In other cases the spinal cord and the skin over it succeed in closing, but there is just enough local retardation to prevent the bony arches of the vertebrae from closing completely. Doubtless among the readers of this book there are a few who have found by running their fingers along the exact middle of the back, that the tips of two or three vertebrae (posterior or dorsal, spines) are incomplete, most commonly in the lowest or sacral part of the spinal column. In this degree spina bifida is a perfectly harmless minor anatomical variation. Such a defect is an excellent example of the way in which abnormalities once extremely puzzling, and therefore subject to explanation by superstitious guesses, can now be traced back (given

sufficient knowledge of embryology) to specific antecedent stages in normal embryonic life.

Mall's group of 163 early pathological embryos contained 12 clear cases of spina bifida. Here then is one of the defects most frequently seen in monstrous births, which is also found to occur in early embryos that could not have survived long enough to reach the status of monstrosity in the usual sense of the term. Mall also found in his collection several cases of incipient *anencephaly*, or faulty development of the brain. When an anencephalic infant is born at or near term, the head and face are so much altered by the long-standing retardation of the cranium as to produce a strange animal like appearance. Such cases form the basis of wild tales about children with frogs' heads and other fantastically misbegotten creatures which Paré and his contemporaries could ascribe only to metaphysical causes. The first conclusion from Mall's work is thus that early dissociation of the embryo on one hand, and late abnormalities of the kinds classifiable as monstrosity, on the other, are simply different degrees of damage, and must be produced by the same set of causes. We must search for the causes in early embryos. Although this conclusion was not entirely original with Mall, his investigation was the first to support it with extensive factual evidence.

In the long list of possible causes of prenatal abnormality, as summarized for example in the passage quoted from Paré in §2 of this chapter, there are two causes, or rather two groups of causative factors, which have always appealed to hardheaded unsuperstitious scientific men. If we define the two groups broadly and in modern terms, we find that one or the other of them has been favored by every one of the serious thinkers who have applied themselves to the problem, from Aristotle down to the present time. They are (1) influences of a physical sort, either mechanical or chemical, acting upon the embryo from outside, and (2)

factors operating from within the egg or the embryo itself, inherited from its parents or at least inherent in the ger-
minal constitution of the egg, or of the sperm cell which
fertilized it, or in the constitution of the embryo which re-
sults from the combination of egg and sperm cell. In short,
a defective or monstrous embryo must be due either to a bad
egg or to a bad environment acting on a good egg. This is
the old problem of heredity versus environment, and it is
just as difficult to resolve in the embryological laboratory
as it is in the world at large. Paré included both possibilities
in his catalog. On the one hand he mentioned the inherit-
ance of deformities, and on the other he listed "straightnesse
of the womb," which implies a variety of mechanical effects
causing pressure upon the embryo. Subsequent writers
specified such factors as malformations of the mother's
uterus itself or of her pelvis, producing literally a too-nar-
row space for the embryo or obstruction by a tumor or by
a twin fetus crowding the available space or the pressure
of corsets upon the mother's abdomen. Every time tight
lacing has returned to fashion, alarmists have arisen, in and
out of the medical profession, to accuse modish young wives
of injuring their unborn babes by drawing corset strings
too tightly. Such mechanical hypotheses of the cruder sort,
which were never proved, gradually gave place to conjectures
about another sort of constriction, namely from adhesions
of the amnion or from loops of the umbilical cord
about the fetus but these conditions were found to be ef-
fects rather than causes of embryonic breakdown. Such
valid objections have been raised to all the theories of sim-
ple physical pressure and constriction that finally they had
to be set aside. When Franklin Mall finished the study of
his own specimens and attempted to formulate an explana-
tion of the abnormalities he had seen in human embryos he
was able to expound a much more subtle theory of damage
by environmental factors, based upon a brilliant and in-

structive series of experimental researches on the embryos of lower animals.

4

Defective and monstrous embryos can be produced from good eggs, by the action of damaging conditions in the environment. This exceedingly important fact was discovered by the French zoologist Étienne Geoffroy St. Hilaire (1772–1844), who experimented upon chicken eggs during incubation. By pricking the embryos through holes in the shell, or by varnishing the shell and thus cutting off the embryo's supply of oxygen, he obtained a large number of anomalies among which were instances of defective heads and of spina bifida. His son Isidore Geoffroy St-Hilaire carried similar experiments back to the earliest days of incubation, with the result that the embryos were dwarfed, or were altogether wanting when the eggs were opened some days after the damage was inflicted.

The eggs of aquatic animals, such as echinoderms (sea urchins, starfishes, and the like), fish, frogs, and salamanders, are relatively subject to experiment since 1890 scarcely a summer has passed at the seaside laboratories without experimentation aimed at producing abnormalities. The problem has attracted many distinguished biologists. The philosophical Hans Driesch in 1892 produced double monsters, very much like human Siamese twins, from sea urchins' eggs by subjecting them to high temperatures. The physiologist Jacques Loeb accomplished the same thing at Woods Hole by exposing the eggs to water of abnormally low saltiness. Edmund B. Wilson did it with eggs of the lancelet, *Amphioxus*, in the two-celled stage of segmentation, by partially separating the two cells by shaking, and Hans Spemann of Freiburg did it with frogs' eggs by tying fine thread around the two-celled egg, thus obtaining two-headed embryos.

Another way of producing temporary injury to aquatic eggs is to put them into water containing dilute chemical agents. The action of salts of lithium upon sea urchins' and fishes' eggs causes a special type of retardation and irregular malformation, analogous to that seen in the nodular retarded embryos of man. Similar "total monstrosity," as Mall called it, was produced by one of his students, C. R. Bardeen, by X-raying the sperm cells of toads before using them to fertilize eggs.

Jacques Loeb discovered that fish eggs subjected to a weak solution of potassium chloride shortly after fertilization developed abnormal hearts which did not beat; such embryos of course became highly abnormal. Another of Mall's students, Henry Knower, was able to remove the heart forming tissues of very young frog embryos by operation under the microscope, and as might be expected he too obtained marked abnormalities in subsequent development. Mall had already seen early human embryos which had developed for several weeks without a heart, forming curious monstrosities.

We owe to Oskar Hertwig of Berlin and to Thomas Hunt Morgan (then at Columbia University, New York) the striking discovery (1894-96) that a 6% solution of common salt, sodium chloride, applied to frogs' eggs at the right stage of development, slows the growth of the neural tube, prevents its closure, and causes spina bifida. When the damage affects the head especially, it produces typical anencephaly (retardation of the brain) analogous to that often seen in abnormal human fetuses.

One more remarkable discovery of the experimental teratologists must be cited before we discuss the application of all this work to the problem of human prenatal abnormality. Charles R. Stockard found that minnows' eggs, treated at one particular early stage of development with dilute solutions of magnesium chloride and other salts exhibited a

very peculiar defect. Instead of developing two eyes, the primordia of the eyes held together during growth, forming one central eye. The salt also retarded general growth and enfeebled the circulation of blood, but many of the embryos survived as cyclopean monsters. This strange special effect is due to local retardation of the frontal part of the brain between the sites of origin of the two eyes. Before Stockard's experiments, cyclopia had been produced in frog embryos by splitting the head region of the early embryo (Born, Spemann), by removing the brain at a very early stage (Ross Harrison), and at a still earlier stage by pricking with a needle the anterior end of the embryonic shield, long before either the brain or the eye-primordia had begun to be visible (Warren H. Lewis). In human embryos the teratological experiments done by nature include a good many defects of the face, resulting from local destruction or retardation during early embryonic stages. Among these, cyclopia had sometimes been known to occur. The cyclopean monster has its one eye in the middle of the face, and the cerebrum is atrophic. Embryos with defects of this degree are usually incapable of long gestation, but they sometimes grow large enough to be objects of attention by the curious perhaps the ancient myth of the original Cyclopes, the one-eyed giants of Mount Etna grew from the birth, or more likely, stillbirth, of such a monster.

A great many experiments of the same general sort have been done with the eggs of birds, especially hens' eggs, but as the reader will easily understand it is more difficult to apply and to control the operative procedures and chemical agents when using eggs that are protected by shells than it is when the objects of study are the eggs of aquatic animals, which are plentiful, easy to handle, and readily exposed to all sorts of experimental conditions. It may be said, however, that most of the common types of monsters that are produced artificially in aquatic eggs have also been pro-

duced in birds' eggs, although with less uniform success. As for the mammals, it is in the first place quite difficult to get the embryos at convenient times and at the right stage of development. This requires elaborate breeding colonies and an extensive knowledge of the reproductive cycles of the various species. In the second place mammalian eggs and embryos are very difficult to get at physically, protected as they are within the uterus. In the third place, it is practically impossible to alter their environment by chemical means (by administering drugs, for example, to the mother) to the slight and exactly controlled degree required to damage the embryos without killing them, for the mother's blood and tissues act as a protective and regulatory defense against all minor variations of salt concentration, acidity, and temperature, or whatever chemical or physical weapons might be tried by the experimenter. For these reasons we are only at the beginning of experimental teratology in the mammals.

Returning to the experiments with aquatic eggs, from which we have learned most, it is important to note that abnormalities are produced by attacking, at just the right time, a region in which profound growth activity is under way. It makes little difference whether the injury is produced by mechanical means, such as shaking or needling the eggs, or by a more subtle physical weapon such as the X ray, by changes in temperature, or by chemical poisons. Of course one of these methods will be more practicable than another in any given case, but the important thing is that all agents operate by disturbing the normal progress of growth and differentiation at specifically critical times. Retardation, for example, of the neural tube when it is about to close produces spina bifida; damage to the front part of the brain at one particular time produces cyclopia, whereas the same injurious agent a little later, when the tissues between the two eye-primordia are firmly developed,

can yield no such spectacular result but only general damage in that region. There is a critical stage of development of the limb-buds, and at such a time a well-adjusted experiment on the embryos of suitable species will produce deformities analogous to human clubfoot.

The brilliant epoch of biological research which I have just sketched was at its height just at the time when Mall was collecting and studying the abnormal human embryos of his 1908 monograph. Men whom he knew personally—Jacques Loeb, Morgan, Wilson, and Stockard—were expertly producing a whole series of anatomical defects and monstrosities in the larvae of echinoderms, fish, and amphibia, while he, in his laboratory, was the observer and recorder of a great and tragic experiment of nature, done upon the embryos of man. The results were all too obviously similar. It was clear to the Baltimore anatomist that the human embryo, no matter how fully protected it is in the uterus, is subject, at the critical times of its development, to influences producing retardation and malformation, as surely as are the aquatic eggs of the experimenters at Woods Hole.

But the human embryo is exposed to no deliberate attack comparable to the instruments and chemical solutions of the biologist. It lies out of sight and out of reach, in the uniformly conditioned environment of the uterine cavity. In the earliest abnormal cases the damage must oftentimes be done even before the mother knows she is pregnant. What then can be the agents of injury and destruction in our own species?

When Mall set himself this question, his only means of answering it was to consider the clinical histories of his cases and to search the specimens themselves for evidence of disease. Naturally he found all sorts of destructive change in the placental tissues. Some of the specimens came from cases of tubal pregnancy, in which of course the em-

bryos were in a highly unfavorable environment. Among the majority which were from ordinary uterine pregnancies, a few showed signs of frank purulent infection. In others Mall or the physicians and pathologists at the hospitals saw what they considered signs of endometritis, that is to say, inflammation of the uterine lining. Strongly influenced by the work of the experimenters, Mall reasoned that just as any egg of a minnow can be made to yield a monster, so every human egg has the possibility of becoming an abnormal embryo if the environment is unfavorable at critical times in its development. He came to the general conclusion that retardation, dissociation, and monstrosity of the human embryo are caused by impaired nutrition, and that this in turn is the result of faulty implantation due usually to disease of the uterus, chiefly inflammation. As far as he could see, the question of heredity versus environment in the determination of prenatal abnormality was answerable entirely in favor of environment.

In the next two sections I am going to show that this final deduction was premature and partly incorrect. The fact is that the pathologists were not in a position at that time to judge the question of maternal uterine disease. The abortion of a human embryo is a damaging process which will show itself in the tissues of both embryo and mother regardless of which is first at fault. The resultant specimens are moreover subject to all sorts of variant clinical conditions which make microscopic diagnosis difficult. The process of sloughing out the products of conception may take days, with resulting injury to the uterine lining; inflammation may occur as a result rather than a cause of the miscarriage; the doctor may have introduced instruments for diagnosis or treatment, producing other damage; in short, the specimens which reach the laboratory can be very misleading. Furthermore, knowledge of the pathology of the uterus was considerably less accurate than Mall realized

when he wrote. At that time (1908) pathologists were not aware of the normal cyclic changes of the human endometrium under the influence of the corpus luteum hormone.^a A classical article on this subject by Hitschmann and Adler of Berlin only appeared in that same year. The diagnosis of mild inflammation of the uterine lining ("glandular endometritis") was being made in many cases that we now know were normal.

The reader should therefore withhold, until he reads farther, acceptance of the idea that human embryonic abnormality is always or usually caused by faulty implantation due to maternal disease but this reservation by no means cancels the value of Mall's masterly extension of human teratology to the early stages. Whatever the malign influences that act upon human embryos, we know from his work that they cannot be peculiar to our own species and that they are ultimately to be explained by observation and experiment within the scope of practical biology and medicine.

5

Among those who remained unconvinced that faulty implantation due to maternal disease is the chief or sole cause of human embryonic defectiveness were biologists who had made a special study of the earliest embryonic stages of animals under natural conditions, influenced neither by laboratory experiments nor by the effects of disease. All such investigators, whether their studies had been upon invertebrates or fishes and birds, had seen defective individuals under circumstances that could not involve a faulty maternal environment, because of the very nature of reproduction in those animals. There can be no question of faulty implantation when one chick in a nestful of incubated eggs fails to hatch, or when a frog's embryo becomes monstrous

a. See Chapter I p. 41.

in the midst of a numerous cluster of eggs all equally exposed to a common environment of pond water. If it be suggested that observations on oviparous animals are remote from the problems of human disease, we must consider that even in mammals defective embryos are known to occur under circumstances which exclude the likelihood of maternal disease. A cow or mare, for instance, occasionally loses one of her embryos, or gives birth to a deformed fetus, as an isolated event in a series of normal births. Still more to the point, animals with multiple litters, such as pig, rabbit, and rat, not infrequently produce a runt or a deformed individual in the midst of a litter of healthy offspring.

The rate of such prenatal loss can be estimated by various methods. The number of eggs discharged from the ovary at one time can be determined, in animals killed during pregnancy, by counting the number of corpora lutea. The reader will recall, from §6 of Chapter I of this book, that when a Graafian follicle sheds its egg, it does not disappear from the ovary but is converted into a solid organ about as large as the follicle, the corpus luteum. The English investigator John Hammond in 1914 found in 27 sows killed shortly after ovulation an average of 20 corpora lutea per animal; this means that an average of 20 eggs was shed. The average litter at birth of the same breeds in England numbers 12. Hammond's figures thus indicate that 40% of the eggs shed failed to reach birth as living pigs. Similar estimates from observations on rabbits by several observers gave prenatal losses from 18% to 33%. J. A. Long and H. M. Evans in their well known monograph on reproduction in the white rat (1922) found 9.6 eggs discharged from the ovaries at one ovulation (average of 50 rats) and an average litter-size at birth (156 litters of the same strain of rats) of 6.4 giving a loss of 33%.

In animals which shed but one egg at each ovulation, the loss of ova cannot well be determined directly, but a some-

what similar calculation can be made by an indirect method. It is well known to breeders that single matings in the horse and cow do not always prove fruitful, even though the mates be fertile. The failures may be attributed to defective sperm cells or eggs, to causes which prevent union of eggs and sperm, to defective fertilization, and to death of the fertilized egg or embryo. If however both the mates are healthy and anatomically normal, and are known to be fertile by the result of previous and subsequent matings, then it is almost certain that the failures are due to trouble with the fertilized egg or the embryo. In a small herd of Ayrshire cattle, expertly managed by a veterinary surgeon (Dr. Dickinson Gorsuch of Timonium, Maryland) there were 8 bulls and 17 cows, all proved to be fertile. During the course of several seasons 54 matings produced 47 pregnancies, giving a 13% rate of failures. Five of the 7 instances of failure were followed by pregnancy after a second mating, and the remaining 2 were followed by pregnancy after a third mating. Similar computations from much larger though less accurately controlled series of cattle and horses, recorded by breeders in Britain and the United States, gave rates of prenatal loss from 20% to more than 50%.

In 1920 a painstaking Scotchman, Arthur Robinson, who was professor of anatomy at Edinburgh, in his Struthers Lecture before the Royal College of Surgeons of that city reported an exceedingly careful study of prenatal mortality in the ferret (*Mustela putorius* a carnivore). His animals, to the number of 165, were killed at various stages from 18 hours after mating until parturition, which occurs in that species on the 42d day. Robinson obtained a prenatal loss, of eggs leaving the ovary which did not result in living young born at term, of not less than 95%. It must be emphasized again that in all the studies on this ques-

tion which have been cited the mothers were presumably free of uterine disease.

Any such computation for the human species is necessarily less precise, but the obstetricians have long believed that the proportion of pregnancies which terminate before birth, including the earliest with the later cases, may be as high as one in three. In the Hertig Rock series of human embryos of the second and third week, now numbering more than a dozen specimens, the percentage of abnormal embryos is about 50%, but this may be higher than in the general population. It should be mentioned, incidentally, that most or all of these abnormal embryos would have been aborted so early, if the cases had not come to operation, that the mothers might not have known they were pregnant.

During the course of investigations such as that of Arthur Robinson it became clear that defective embryos may be found in uteri which are free of infection and other pathological conditions, and that in animals which bear more than one embryo at each gestation normal and abnormal embryos may be found in the uterus at the same time. Furthermore, abnormality or degeneration may occur at any time, even in the first days of gestation. Embryologists who have seen many early embryos of mammals have occasionally found abnormal embryos before implantation. I myself reported in 1921 a pig blastocyst, still unattached, which bore a little tumor instead of a normal embryonic disc, perhaps the earliest mammalian embryo yet reported which may properly be termed a monstrosity. It was found in a healthy uterus.

To such isolated observations Arthur Robinson made a valuable addition, in his work upon the ferret, by classifying his cases of abnormality according to the stage of pregnancy at which they were detected. He found that in 57 animals studied before the 8th day of pregnancy 16% of

the ova were missing or unsegmented. Other embryos became abnormal at later stages. Microscopic examination of the uteri proved them to be free of disease, except that when embryonic death occurred after implantation, Robinson found changes in the lining of the uterus similar to those described by Mall in human uteri containing abnormal embryos. He believed that in his ferrets defective embryos had become faultily implanted, rather than that faulty implantation caused embryonic defects. He suggested that these failures of fertilization and of development are due partly to inability of the eggs and sperm cells of certain individuals to unite at all with each other, and partly to the production of abnormal embryos by the union of certain eggs and sperm cells.

In the summer of 1920 I found myself in a celebrated laboratory devoted to the study of heredity, the Department of Genetics of the Carnegie Institution of Washington, at Cold Spring Harbor, Long Island. The Director, Dr Charles B Davenport, was himself interested, although from another standpoint, in the question of prenatal loss. In trying to explain some peculiar features of inheritance in human families, Davenport had been forced to suppose that some of the mortality in utero must be due to a constitutional incapacity for development on the part of certain embryos which have become implanted in a healthy environment. By way of testing this supposition he made a number of counts of corpora lutea and embryos of swine, choosing that species simply because the pork business has made it the easiest of all mammals from which to get embryological material in quantity lots. The result of Davenport's counts was similar to those cited above from Robinson and others.

I was at the time in the midst of an extensive study of the physiology of reproduction in swine, and was in possession of information which I thought might help to carry the dis-

cussion farther In the first place, the pig happens to be especially favorable for this sort of study, because the mode of placentation is very simple. As explained in Chapter I, §10, there is no interlocking of fetal and maternal tissues, and it is therefore very easy to decide whether damage to the tissues of the implantation site is on the maternal or the embryonic side. The second way in which I hoped to make a contribution to the question requires somewhat fuller statement. I explained in Chapter I that successful implantation of embryos involves the exact completion of a series of changes in the lining of the uterus by which it is made fit to receive the embryos these changes are caused by a chemical secretion (a hormone) of the corpus luteum The understanding of all this was just then being worked out in various animals It had become known that unless the uterine lining is in the progestational state, as shown in the right hand pictures of Plate V, the embryo will not find a suitable environment when it arrives in the uterus In view of this fact, those who demand the fullest proof of a normal uterine environment might well raise the question whether Robinson and other workers had said the last word when they stated simply that they found the uterus normal, healthy, or free from infection It might be normal and healthy in a general way, and yet through some imaginable disturbance of function not have reached that stage of tissue change which is necessary for successful nourishment and implantation of the embryos. A field may be drained and cleared and yet not be ploughed and fertilized sufficiently to sustain an exacting crop I had been studying the uterine cycle in the sow, and having just published a day to-day description of the microscopic state of the uterine lining in the first weeks of pregnancy, thought myself prepared to decide in a given case, better than could just then be done in any other species, whether or not the uterine environment was functionally normal as well as merely free from disease.

Dr Davenport provided me with his blessing, a communication ticket to New York City, and an enthusiastic young assistant, Dr Clyde Keeler. Adding to the specimens he and I collected at the packing house in New York a small number obtained later in Baltimore, I examined 535 pregnant uteri containing 9,774 embryos and fetuses in all stages of development. In the earliest pregnancies the uteri were washed out with salt solution and the washings were searched under the microscope. By grouping all the specimens according to the stage of pregnancy and tabulating the numerical proportion of surviving embryos to the corpora lutea in each group, it was possible to work out the rate of loss. To make a long story short, I found that at least 10% of the eggs did not divide at all; another 10% developed into blastocysts and then degenerated and still others, amounting to another 5% to 10%, died or became visibly abnormal after the blastocyst stage, some of them during implantation, others at various stages of pregnancy. Only about 70% of the eggs were represented at term by living pigs. It must be emphasized that I tabulated only cases in which some of the embryos were normal; in other words, the dead or abnormal embryos in question had come to grief in the same uterus with healthy litter mates. All uteri containing embryos up to and including the critical stage of implantation were subjected to microscopic examination and were found to be functionally normal. Whenever at later stages an abnormal embryo or fetus was found, that part of the uterus in which it lay was carefully examined and if necessary sectioned for microscopic examination. No maternal disease was found in these cases; the uterine wall around a dead embryo was like that around the healthy, growing litter mates.

The commonest type of abnormality found in these pregnancies was characterized by general breakdown and maceration (i.e., slow softening with ultimate disintegration).

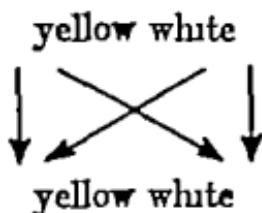
Other abnormalities included cleft palate, absence of the tail, and amorphous (formless or nodular) embryos. In several of the earliest cases I found undivided eggs surrounded by sperm cells.

These observations show beyond doubt that a large part of the total prenatal mortality in the sow occurs in the complete absence of maternal disease as far as can be determined by direct microscopic examination, and in uterus which must be functionally normal, with all the hormone mechanisms in good order, for they are at the same time carrying other embryos through the normal course of development. It should be mentioned that there are undoubtedly also some cases in which maternal disease plays the decisive part. I have seen a few instances (not included in the foregoing summation) in which the uterus was infected with pus-forming germs, causing death of all the embryos. This is of course a very different matter from the death or abnormality of a single embryo or two or three scattered through a uterus among normal litter mates. Most of the human defects in which we are interested are without doubt comparable to the latter class, for they usually occur as individual cases intercalated in a family series of normal births.

6

We are forced, then, to suppose that in almost every litter of pigs, and presumably among the offspring of other mammals, there are good embryos and there are also bad ones which carry within themselves the hidden causes of their own destruction or defectiveness, and are doomed even though they receive the advantages of a good environment in the uterus. How is this to be reconciled with the evidence from experimental embryology cited in §4 above, which proves that every egg contains the possibility of abnormal development under the influence of harmful agents in the environment?

In the same year in which F P Mall's monograph on the causes of human monsters appeared (1908), the French biologist L. Cuénot discovered a case of hereditary transmission of an embryonic defect which is much subtler and more instructive than his fellow countryman Paré's example (quoted at the beginning of this chapter) of "crooke-backt produce crooke-backt, lame produce lame, flat nosed their like." Cuénot's findings were amplified by the American geneticists W E Castle and C C Little what I cite here is the work of all three. There is a kind of tame mouse, bred by fanciers, which has a yellow coat. This characteristic is dominant in breeding that is to say, if a yellow mouse is mated with one of another color, say white, all the offspring are yellow. But the second generation mice, having one white parent, carry the hidden (recessive) potency of producing white offspring. If two such mice, each carrying a recessive inheritance factor (gene) for white coat color, are mated together, we expect from the principles of Mendelian inheritance that one-fourth of the offspring will inherit the yellow coat from both parents and will of course be yellow, carrying no genes at all for white; one-fourth will inherit white coat from both parents, and will be white, since they carry no genes for yellow, two-fourths will inherit yellow from one parent and white from the other, and will be yellow but will carry the recessive gene for white. Thus the whole group of offspring will contain 3 yellow to 1 white. This expectation is shown diagrammatically as follows:



1 yellow yellow + 2 yellow (white) + 1 white-white

A similar result occurred in Mendel's original cross of tall with short sweet peas and has been confirmed in thousands of crosses in all sorts of plants and animals in which simple combinations of a dominant with a recessive character have been followed out. In the case of the yellow mouse, however, Cuénot noticed a different outcome. The families of yellow (white) mouse pairs average only two yellow-coated to one white-coated offspring. When the yellow offspring are themselves tested by mating together, one-third of their offspring are in turn white instead of one-fourth. None of the yellow-coated mice, in fact, ever give evidence of being pure-bred for yellow. It is obvious therefore that the expected yellow yellow mice, which should make up one-fourth of the total offspring, are not being born. There must be something incompatible with life in a double inheritance of the yellow-coat gene, not necessarily the color itself, but some factor that is inherited along with the genes for yellow. Counts of the families of these mice support this conjecture, for the average number in a litter is about one-fourth less than in out-crosses of the same mice and finally, the New Haven embryologist Kirkham found in 1917 that about one-fourth of the embryos die in utero at or soon after the time of implantation.

The case of the yellow mice is a good example of a *lethal gene*, an inheritable factor which causes death of the individuals which receive it undiluted by the corresponding nonlethal gene from the other parent. In the fruit fly *Drosophila* and the other animals and plants which have been extensively studied by geneticists many such lethal factors are known, and also many others which are merely detrimental rather than lethal, since they do not kill the affected individuals but only make them abnormal within the range of viability. These various harmful factors may take effect at any stage of life. Some are known which produce imperfect eggs or sperm (in plants, defective ovules or

pollen), thus preventing these germ cells from even completing the process of fertilization. Others operate upon the early embryo, as in the yellow mouse, and still others come into play late in embryonic life or even after birth. The rare human disease called Huntington's chorea exemplifies the action of a lethal factor which does not take effect until late in adult life.

Lethal and detrimental genes are also quite various in the nature of the disturbances they produce, they may cause retardation of this or that phase of development, or an anatomical deformity, or they may upset the chemical function of one or another tissue of the body.

The problem of lethal and detrimental hereditary factors in mammals has in recent years been attacked by several of the leading geneticists, including especially Sewall Wright of Chicago, H. Grueneberg of London, C. H. Danforth of Stanford University, E. Carlton MacDowell of Cold Spring Harbor, and L. C. Dunn of Columbia University. I am indebted, for many of the facts cited in the next few pages, to Dr Dunn's Harvey Society Lecture of 1940 and other recent papers by himself and colleagues. In the small, prolific laboratory mammals such as mice, rats, and guinea pigs, quite a number of embryonic and congenital abnormalities have been found to occur as hereditary characters. As the development of the affected individuals has been worked out, the disturbances have been found to be due basically to failure to attain the normal degree of development at a given time, either in general growth or in one or another special region of the embryo, but since the growth of the separate parts is partly dependent upon the orderly progress of the whole body, these retarding influences may not only prevent the growth of a given part but they may cause the regression of a part after its more or less normal primary development, or, on the

other hand, permit overgrowths by upsetting the local balance of growth.

Most types of abnormalities which have been traced to their first appearance are found to begin early in development. The more they are studied the more they are seen to represent, so to speak, orderly disturbances of the normal patterns of development. This point will be clearer a little later when we discuss the organizer system of the embryo. One example will serve to illustrate what is meant. Sewall Wright reported in 1935 a strain of guinea pigs which carries a hereditary factor affecting the front and hind feet. Animals which inherit this gene from only one parent tend to have one extra toe on each foot apparently there is a local stimulus to excessive growth which takes effect in this way. Those offspring, however, which inherit the factor from both parents develop into monsters, most of which die as young embryos only a few surviving to be born at term. In these latter the legs are short and distorted, with paddle-shaped feet the eyes are rudimentary and the head misshapen. J. P. Scott, who studied the embryology of these guinea pigs, finds that the first visible abnormality is excessive growth and, at the same time, arrested differentiation of form of parts which are growing most rapidly at about 17 days of gestation (total gestation period 65 days). The abnormal heredity, in double dose, seems to stimulate general growth at that special time. Parts which would just then be attaining definitive form, in particular the fore and hind feet, are made to grow faster than they can differentiate. If this imbalance of growth is severe enough, the embryos die but if they live, the growth impulse subsides in that region and the part is left in an embryonic state while other regions grow in their turn. Similar researches have shown that many of the types of embryonic or congenital defects commonly occurring in the human race for instance

spina bifida and anencephaly, cleft palate, deformities of the face, hands, and feet, and imperforate anus, also occur as hereditary characteristics in the laboratory animals, in which they can be investigated by genetic analysis and embryological study. Although we cannot experiment with our own species, the inference is clear that, as in other animals, anomalies are often the products of bad eggs in a good environment.

But lest the pendulum of our thought swing too far, let me next cite another instructive case. There is a well known hereditary anomaly of fowls called rumplessness, in which a few vertebrae at the end of the spinal column, in the region of the sacrum and tail, are suppressed. This is inherited as a simple Mendelian character. L. C. Dunn, and also Walter Landauer of the University of Connecticut, pointed out the occasional occurrence of spontaneous cases of rumplessness which are not hereditary. Once, in 1932, when Charles Danforth of Stanford University happened to be incubating hens' eggs for experimental purposes, three rumpless chicks turned up in one lot of eggs. Unable to accept this as a coincidence, Danforth guessed that some disturbance during early incubation might have produced the defect, and therefore he tried varying the incubator temperature. Incubating, in various trials, 52 eggs from normal parents (i.e., fowls not carrying the gene for hereditary rumplessness) he obtained 4 cases of the deformity, all of them from eggs which had been subjected to fluctuating temperature during the first week of incubation. The important thing about this experiment is that a defect, anatomically the same, and known to depend upon retardation of growth at the caudal end of the embryonic body during the first days of incubation, has been shown to occur (1) as a hereditary character of the simplest kind, (2) as a seemingly chance variation which is not hereditary, and (3) as the result of injurious environmental conditions acting upon normal em-

bryos. Thus either a bad egg in a good environment, or a good egg in a bad environment, can become abnormal in the same way. This is a remarkable thing, that exactly or almost exactly similar injuries, often of a highly specific sort, and dependent upon very special maladjustments at very particular times in embryonic life, can result from such dissimilar causes. How this can be is to a certain extent explained by the theory of organizers, which I shall next discuss.

The concept of the organizers is best introduced by the story of the first experiments upon which it is based. These concerned the development of the eye in amphibian embryos. In all vertebrates the eye begins as an outgrowth from the side of the brain, which takes the form of a cup connected to the brain by a stalk. The stalk becomes the optic nerve; the cup forms the sides and back of the eyeball. As the cup grows out, it comes very close to the outer layer of the embryo, the ectoderm, and a round area of the latter becomes thickened and sinks a little way in toward the open part of the optic cup to become the lens of the eye. About the year 1900 the German zoologist H. Spemann tried the experiment of destroying the primordium of the optic cup, in early embryos of the newt, Triton, by a cauterizing needle. Although the eye rudiment usually regenerated after such an injury, it remained small and deeply situated, not approaching the ectoderm. In these cases no lens was formed. In the spring of 1903 Warren H. Lewis of Baltimore extended Spemann's experiment by applying a much more elaborate form of experimental surgery to frog embryos. Working with larval tadpoles only a few millimeters long, under the microscope, he was able with very fine needles to remove the eye rudiment or to transplant it. If the optic cup was removed, no lens was formed. If the eye regenerated after the injury as it often did, it formed a lens only if it grew large enough to make contact with the ecto-

derm at the proper stage of development. If the optic cup was transplanted to a point under the skin at a distance from the region where lens tissue is normally formed, a lens was induced from ectoderm at the new site. In other experiments Lewis left the optic cup in place but removed the ectoderm over it and substituted a graft of ectoderm from another region, for example the abdomen. Again a lens formed from tissue that normally would have provided not lens material but abdominal skin. In one experiment, skin from the abdomen of a wood frog tadpole (*Rana sylvatica*) was grafted over the optic cup of an embryo of the pickerel frog (*R. palustris*) and was converted into a lens in spite of the difference in species as well as in the site of origin. It is clear that in these frogs, normal development of the lens is dependent for its start upon some sort of stimulus arising from the optic cup.

Spemann then thought of looking for earlier instances of this sort of induction and soon found that in very early amphibian embryos there is a primary organization center, at a point where the head and trunk tissue is first formed (in technical words, the dorsal lip of the blastopore). The tissue of this region, if removed and implanted, for instance, on the side of the body of another early embryo, will induce the ectoderm of the host to form an extra neural tube, often accompanied by somites and other tissues of the head and trunk region. It follows from experiments like this that in normal development the primary organization center calls forth the development of the primitive brain and spinal cord. The optic cup, which forms from the brain, becomes in turn an organizer of the second rank, calling forth the lens. There is evidence that the lens itself acts as organizer to elicit formation of the cornea from the outer ectoderm of the eye region.

A large number of such induction phenomena has been discovered by experiment, largely upon the embryos of am-

phibians and birds. The subject has engaged the efforts of many experimenters and has accumulated a vast literature. Some of the main facts are of especial interest for our present discussion. One of them is that a given undifferentiated tissue, as for example the ectoderm of the eye region in our first example above, can respond to an organizer only during a limited period. It must have reached a certain stage of differentiation before it can respond and later its character becomes fixed, so that it can yield only a more limited type of response. The organizer tissues also operate only during critical stages, losing at a later time their power to induce changes in the indifferent neighboring tissue. Speaking broadly, the earlier organizer centers are general in their action, inducing tissues which are of broad extent and importance, such as the neural tube. As the embryos take form, the organizers of secondary and tertiary rank become more local and the organs induced are more specialized. I have given the merest sketch of a very complex subject and it should be added that practically none of the work has been carried out as yet on mammals but we may provisionally accept the thought that in all vertebrates, including man, the development of the animal body from the egg is guided by the action of a succession of organizer centers, getting more and more specialized and more local as they succeed one another until the whole complex system of tissues and organs has differentiated itself out of what was once an egg, of very general potency. As a crude parallel, imagine a little workshop started by one man of all around talents. His first employees learn the business from him and as the factory grows they become department heads, each organizing his own part of the work until all sorts of specialized workers are developed capable in their turn of developing new employees but only in their own narrow fields.

The action of embryonic organization centers is due to chemical substances which they produce and transmit to the

neighboring responsive tissues Many types of induction have been elicited experimentally by implanting bits of boiled tissue from the organizer regions, or by using chemical extracts Readers who wish a detailed analysis of the subject will find it in Joseph Needham's *Biochemistry and Morphogenesis* (1942) This brief sketch will perhaps, however, suggest what a flood of light the theory of organizers throws upon the problem of embryonic defects, by showing that anything which interferes with the process of organization at a given point will necessarily produce much the same sort of injury

This is well illustrated by experiments on the production of cyclopia, published 1934 to 1937 by H B Adelmann of Cornell University It will be recalled from §4 above that embryos of aquatic animals having one central eye have been produced by the action of chemical agents and also by physical damage to the head region of the early embryo Adelmann first repeated on salamander eggs the experiments with dilute solutions of magnesium and lithium chloride, and found that with the microscope he could locate the site of the earliest damage in a small median portion of the mesoderm near the front of the head This is the anterior part of the primary organizer tissue In later experiments Adelmann excised the same tissue from normal embryos and obtained cyclopia. Thus he showed that both the chemical solutions and the surgical injuries of the earlier experimenters had produced this effect in the same way that is to say, by damaging the organizer region which guides the separation of the optic primordia.

A great many observations on the effects of lethal and detrimental genes in mammals indicate that these hereditary agents also produce their injuries by disturbing the organizer system Indeed, the action of the genes is believed to be effected by the production of catalysts, substances

which speed up chemical reactions, or of inhibitory substances, and thus there may be little difference as far as the effects on an organizer center are concerned, between the action of a deleterious gene and of a toxic solution applied by the experimenter. It should be remembered also that injury to the reactant tissue (that which responds to the organizer) will cause failure of embryonic growth just as much as if the organizer is disturbed, so that the harmful agencies have two targets upon either of which they may act in one case or another. Thus any given structural defect may be the result either of an hereditary or of an environmental cause. Since the development of any species must be guided by a succession of organizing processes, each of which is subject to disturbance, the possible abnormalities will not occur in random assortment but will tend to fall into classes and types corresponding to the most critical stages and regions in development. Injuries inflicted early will in general produce widespread disturbance of growth those affecting the primary organizer, or the early indifferent tissues it organizes, will cause lesions of the central nervous system such as spina bifida and anencephaly. Late injuries will tend on the other hand to produce local defects. A relatively slight disturbance either of the environment or of genic action, attacking the organizer reactor system at a critical time, may produce serious disturbance.

7

Since it is not possible to study the nature of human embryonic defects by direct experiment, we are compelled to do the best we can by observation and by comparison with the results of experiments on animals. From what has been said in previous sections of this chapter, there must be a whole series of possible causes. Let us draw up the list unlike Ambroise Paré, I shall not begin with the name of God

nor end with the Devil, for science has learned in the past 400 years that the forces of good and evil in this world take effect through natural causes.

A. Defects of fertilization	1. Irregular fertilization
B. Defects of the maternal environment	2. Faulty transportation 3. Failure of the hormone system 4. Mechanical disorder of the uterus 5. Infection of the reproductive tract 6. Infectious disease of the embryo 7. Toxicity and 8. Nutritional defect of the uterine environment
C. Defects of the egg, the sperm cell, and the embryo	9. Genetic defects 10. Nongenetic constitutional defects

1. Irregular fertilization may well account for the condition of those ova which do not segment at all or which die after a few cell divisions. It has been suggested that in mammals the egg may occasionally be fertilized by more than one sperm cell and thus be rendered incapable of normal segmentation. Such an irregularity has often been seen in aquatic eggs. Among a score of recently fertilized eggs of the sow which I once sectioned I found two instances of double fertilization. Paré would claim this as a case of "excess of the seed."

2. It is conceivable that the mechanism for transporting the egg from the ovary to the uterus may at times fail in such a way as to delay the arrival of the fertilized egg at its proper destination, the uterine cavity. This would amount to giving it a temporary unfavorable environment and the case would really be classifiable under 7 or 8, below. In human tubal pregnancy the fertilized egg is retained in the oviduct (Fallopian tube) and although it is able to develop at first, sometimes for several weeks, it stretches or ruptures

the tube and so brings on an acute termination. The frequency of abnormality in such embryos is very high nodular embryos, *spina bifida* and other serious defects are frequent. This seems to be a clear case of defectiveness due to faulty environment. We do not know, by the way, the cause of tubal pregnancy no investigator has succeeded in reproducing the condition in animals.

3 Failure of the hormone system, and in particular of the corpus luteum, which normally takes a great part in producing a suitable environment for the embryo, has been shown by direct experiment in animals to be a cause of early embryonic death. It could hardly lead to defective growth of the living embryo except by the rare occurrence of a transitory partial hormone failure at a critical time in the life of the embryo. As far as human gestation is concerned, failure of the hormone mechanism controlling the uterus remains a hypothetical possibility in the causation of disturbances of the embryo.

4 Mechanical disorder of the uterus is seen in women with malposition, deformity, or tumors of the uterus, giving insufficient space for development of the embryo. Paré would have called it "strangeness of the womb." The usual result, if an embryo succeeds in getting itself implanted, is expulsion at the second or third month. An embryo developing under such unfavorable conditions with regard to space is likely, as in tubal pregnancy, to become anatomically abnormal because of poor conditions which affect its growth.

5 Infection of the uterus with disease germs can certainly make trouble for the embryo, but as with the two previous categories, is more likely to cause outright destruction than structural abnormality. It would be rare to have inflammatory disease sufficiently mild to permit fertilization and implantation, and yet serious enough to disturb the health of the embryo. This is the cause which Mall

put first in his thinking, but it is now regarded as almost negligible as a cause of embryonic abnormality and monstrosity. It is of course a relatively frequent cause of total failure of reproduction, i.e., sterility, by preventing fertilization and implantation.

6 The idea that the early embryo may suffer damage by acute infection with disease germs is a novel one. It is well known that some kinds of microorganisms pass through the placenta and invade the fetus. The most important instance is that of syphilis, which is one of the most serious causes of abortion or premature labor. The organisms of this disease produce damage of the placenta, impairing the nutrition of the fetus, frequently causing its death. In case the fetus survives, the disease produces serious lesions of the skin and internal organs of the infant. This, however, is a disease rather than a state of embryonic abnormality of the sort under discussion in this chapter. The same statement applies to smallpox of the fetus, when the mother has the disease during pregnancy and transmits it through the placenta—a rare but well-authenticated occurrence. In a number of instances of other diseases attacking pregnant women, the germs have been found in the tissues of the infant, without obviously harmful effect. In view of the extraordinary story I have to tell next, it is of great interest to know that experiments with rabbits and guinea pigs have demonstrated that the exceedingly small infectious particles of a number of the so-called virus diseases can pass through the placenta into the embryo.

In 1941 the Australian ophthalmologist, N. M. Gregg, reported a series of cases of congenital cataract occurring in babies born between December, 1939, and January, 1941. With few exceptions the mothers of these infants had suffered during the early stages of pregnancy from a disease which had been epidemic in South Australia at the time, and which was considered to be a slightly atypical form of ru-

bella ("German measles") Dr Gregg could not escape the thought that the mothers' illnesses had in some way been responsible for the damaged eyes of the babies. Following the announcement of these circumstances, the medical profession of South Australia organized itself under the National Health and Medical Research Council for a systematic investigation directed by Dr Charles Swan of Adelaide. The results of this study, published in September, 1948, confirmed Gregg's hypothesis by showing that twenty five patients who had contracted rubella during the first two months of pregnancy all without exception later had infants with congenital abnormalities either of the eyes or of other organs. Four out of eight patients who contracted the disease in the third month of pregnancy had congenitally defective children. When the mother's illness occurred after the third month, the infant was not harmed.

The various lesions observed in these babies were congenital cataract, sometimes with microphthalmos (reduced size of the eye) deaf mutism, defects of the heart and microcephaly (abnormally small head and brain). In all probability, the infectious agent of the disease, which is believed to be a filterable virus, passes through the placenta and affects the organizing tissues of brain, eye, ear, and heart.

Because any such association of embryonic defects with German measles had never been thought of before, the Australian physicians were inclined to think that the virus responsible for this recent epidemic and subsequent sporadic cases may have undergone some alteration of virulence or other biological change, thus newly acquiring its dreadful power to harm the infant.

It appears, however, that the same circumstances are occurring in the United States. Dr Frank B. Walsh of the Wilmer Ophthalmological Clinic of Johns Hopkins Hospital, to whom I am indebted for calling my attention to

the Australian reports, has been quick to follow up this matter. He and his colleagues of the Children's Clinic, Dr Helen B. Taussig and Dr Harriet Guild, have already collected several exactly similar cases which originated in Baltimore. In the course of their inquiries, Dr. Walsh sent reprints of the Australian paper to a medical colleague in the Wilmer Clinic, who recounted the remarkable fact that one of his patients had recently had the misfortune to bear a child with congenital cataracts after having rubella during pregnancy knowing of two similar cases among her own acquaintances, she had arrived at the same explanation as had the medical men on the other side of the world.

In all these American cases, like those in Australia, the damage was produced by attacks of rubella during the first two or three months of pregnancy. It seems certain that in the later months no harm to the infant occurs. A good deal of further study will be required before we can know whether this tragic sequel of German measles is a constant effect under the circumstances, or merely something which happens to be occurring at the present time as the result of a temporary change in the virus of rubella, like those which make scarlet fever and influenza, for example, more dangerous one year than another. The Australian investigators naturally call for the redoubling of efforts in the laboratory to produce a protective inoculation against the virus of rubella but this is not something that can certainly be done soon. Meanwhile, pending exact knowledge as to the constancy of the danger, any doctor confronted with a case of this disease in early pregnancy may be called upon to consider terminating the pregnancy, and thus will face a problem in law, theology, and medical judgment to which a fully informed answer cannot yet be given.

7 When I first made a list like this, in 1923, in connection with the problem of prenatal defects in the pig, I said that toxicity of the environment in which the embryo de-

velops, sufficient to produce disturbances of the mammalian embryo comparable to those which the experimenters have made in aquatic eggs (§4 above), was purely hypothetical as far as mammals were concerned. Some writers had supposed that in mammals there may be chemical toxins, reactions of immunity, defective oxygenation in the reproductive tract, or other similar causes of harm to the embryo in utero but no such case had been proved. In recent years, however a previously unsuspected cause of disease of the unborn human infant, involving an immunity reaction, has been discovered. The problem has been analyzed chiefly by Philip Levine of New York, bacteriologist of the Newark (N. J.) Beth Israel Hospital. What is said here comes from Dr. Levine's articles. Everyone is familiar with the fact that the animal body reacts against certain foreign materials belonging to the class of proteins, if they get into the blood or tissues, by forming chemical substances ("immune bodies") which act defensively against the intrusive materials by altering their chemical or physical nature. Thus the toxin produced by the germs of diphtheria causes the body to make an antitoxin which combines with the toxin, forming a harmless compound. Red blood cells from a given species introduced into an animal of another species similarly elicit the production of immune substances which cause the foreign blood cells to become clumped or "agglutinated." The human species, as has been known for years, is divided into groups characterized by the presence of substances in the blood cells which call out immunity reactions if the blood is used in transfusions, clumping the cells and clogging the capillary vessels. This is why prospective donors of whole blood must be "typed," i.e. tested to see which group they belong to before their blood can be used for a given patient.

In 1940 the celebrated immunologist of the Rockefeller Institute, Karl Landsteiner published with his associate,

A. S. Wiener, the curious discovery that if a rabbit is injected with the blood of a rhesus monkey, its blood in turn develops an immune substance which will agglutinate not only the monkey's blood but also that of about 85% of humans. Thus there must be in human blood a substance which is also present in the monkey for convenience the investigators called it "Rh" (from *rhesus*). The Rh factor is inherited as a Mendelian dominant gene, and there are three classes of people, namely those who inherited the Rh from both parents, those who inherited it from only one, and those who do not have it at all. Wiener and Peters soon showed that human patients lacking the Rh factor (they are designated as Rh—), if given repeated transfusions of Rh+ blood, develop agglutinating substances against the Rh+ cells.

In the same year in which these facts were announced, Levine and his coworkers Katzin and Burnham by a brilliant piece of detective work traced the origin of a serious disease of late fetuses and newborn children, called *erythroblastosis* to the Rh factor. Levine and Stetson had published in 1939 the case of a woman who bore a stillborn fetus, and who was incidentally found to have in her blood an immune substance (agglutinin), of a previously unknown type, against the blood of her husband, so that a transfusion with his blood during her obstetrical illness caused a typical reaction with chills and pains. Reasoning about this case, they proposed the idea that the infant must have inherited the immunizing factor from its father and then in some way immunized its mother with it. As was subsequently demonstrated, the substance in question was actually the Rh factor, and therefore this woman was the first human being in whom it was detected, even though at the time of her illness the name had not yet been introduced. Proceeding from this start, they found that the child of a Rh— mother by a Rh+ father (which is always Rh+ the

factor being dominant in inheritance) does indeed sometimes immunize its mother against Rh+ blood cells. The English investigator F. Stratton has recently reported finding the blood of a 48 mm embryo, approximately 11 weeks old, positive for Rh. It is supposed that a few fetal blood cells or particles of red-cell substance may slip through the placenta into the mother's blood stream, giving her, so to speak, a minute but possibly more or less continuous transfusion. When her blood has formed a sufficient amount of anti-Rh immune substance, this passes back through the placenta to the child's blood. As stated in Chapter I, §8, it has long been known that certain immune substances readily pass the placental barrier. The child is now receiving a substance which damages its blood cells, and it develops serious and indeed often fatal disturbances of its blood forming organs. Frequently, however, one or two pregnancies are required to build up dangerous amounts of anti-Rh substance in the mother's blood, and thus only the later pregnancies will be affected. This is no mere technical play thing of the laboratory; it is the cause of a dead baby in about 1 out of every 300 deliveries, and is probably responsible also for a certain number of early fetal deaths terminating in miscarriage. When the father is homozygous for Rh (i.e., he inherited the factor from both parents, so that all his sperm cells carry it) the chance of trouble after the first pregnancy or two becomes very great. For unknown reasons, however, the disease does not occur in every family in which the genetic combination is appropriate for it.

A distressing fact about erythroblastosis is that the affected infants are in no wise originally defective. The Rh+ infant remains normal if its mother is Rh+. The parents of an embryo that is lost by spontaneous abortion are often, and legitimately, consoled by the physician with the thought that this was in all probability the end of a life already marred by genetic insufficiency or by some accident of

development but not even such cold comfort as that can be offered the mother of an erythroblastotic child, who finds herself unable to bear her own offspring unharmed. The only hope lies in the development of the science of immunology to the point where these tragedies can be reliably predicted and protection afforded by treatment. As usual when a discovery of this sort is made, many facts previously obscure become intelligible, and there are hints of other immune reactions harmful to the fetus, involving other blood-group factors. The whole subject is now under very active investigation.

From the theoretical standpoint, fetal erythroblastosis is a striking example of damage to the child in utero by an unfavorable environment. Because, however, the child causes its mother to be harmful to it by reason of its own inheritance of the Rh factor, the situation can also be ascribed indirectly to heredity.

7a. One of the ways of subjecting embryos to an abnormal environment, used by those who make experiments upon aquatic eggs, is radiation with X rays and radium. These physical agencies are also of course used for treatment of human disease, and once in a while a pregnant woman is radiated. There is at least a theoretical possibility that a large dose of radiation, striking an early embryo in utero, might produce embryonic defects. Some experimental evidence for this possibility has been brought out by the experiments of H. J. Bagg on mice, but the actual occurrence of such harm to human infants has not, in my opinion, been convincingly proved.

8 Specific nutritional deficiencies acting upon the infant in utero remain a more or less hypothetical cause of embryonic death and defect. Very general and severe metabolic upsets, due for example to starvation or to severe thyroid disease, can of course terminate the pregnancy, but the embryo is well protected against minor disturbances of

nutrition by the conditioned chemical adjustments of the mother's body. Lack of calcium in the maternal diet may show itself in calcium deficiency of the child's bones and teeth. In laboratory animals pregnancies can be terminated by deficiency of Vitamin E. Josef Warkany and colleagues, of Cincinnati, report the occurrence of severe skeletal deformities in the offspring of pregnant rats fed on a diet deficient in certain respects. To the best of my knowledge, however, specific nutritional deficiencies are not a common cause of anatomical abnormalities of human embryos and probably not of prenatal death.

9 The frequent occurrence in humans of defects due directly to genetic factors, i.e., lethal and detrimental genes, cannot be doubted after the clear demonstration of their existence in animals, as recounted in §5 above. They are difficult to analyze by the methods of genetics because of the slow generations and small size of human families. An argument sometimes arises as to which side of the family contributed the baby's big feet or receding chin. There is no use indulging in any such debate over the obscure detrimental genes which operate against certain embryos. It will be a very long time before enough is known about human heredity to enable a prediction of unfavorable human crosses, except in a few obvious cases. We have no idea how many unseen lethal factors are being carried in the human race, doing no harm until an unfortunate mating gives them a chance to act. I hasten to remark once more, lest the gloomier aspects of the subject unduly depress prospective parents among my readers, that after all we are talking about a minority of cases. A great many perfect babies are being born every day! If by any chance these pages are read by an expectant mother let her consider that once implantation is well established the odds are overwhelmingly in favor of a normal delivery and a healthy baby.

10 The list concludes with an item which is tentative

and somewhat vague. I think it possible that there are sometimes constitutional flaws in the egg or the sperm cells or in the embryo as it grows, which are neither inherited nor inflicted from outside. In anything so complicated as the development of an animal there must be countless opportunities for small steps to go wrong, not because of a downright bad environment, nor because an essential gene is missing or misbehaving, but simply because something just doesn't click at the right time. Such an accident of development, if too great to be healed by the processes of growth, would set up a sporadic, noninherited constitutional defect. One well known example that cannot at present be classified in any other way is the so-called Mongolian deficiency, characterized by mental retardation, with slanting eyes and usually with anatomical defects of the heart. Children so affected are often the first or the last in an otherwise healthy family there is no clear evidence of heredity and no known maternal condition to which the defect can be ascribed.

The theoretical difficulty in setting up a class of non-genetic constitutional defects is that we do not know how to draw the line between these, if they exist, and disturbances due to faulty environment or to genic deficiency. The environment provided by the mother's body is always of course fluctuating slightly in spite of all the regulatory devices of nature to keep it uniform we do not yet know, for instance, whether a day of high fever or some toxic state affecting the early embryo at some very critical moment in growth might not upset the process of organization. An other difficulty is illustrated by L. C. Dunn's analysis of a strain of rats in his colony which carries a factor producing shortness of the tail. The defect, though positively known to be hereditary, shows itself only sporadically. Breeding experiments suggest that the hereditary factor merely produces a certain sensitiveness, so to speak, of the process of organizing the tail region, so that minor variations of en-

vironmental conditions such (conjecturally) as the mother's temperature or metabolic state can affect the tail if they happen to occur at the right time. Abnormalities of man, produced by a gene of this type, might entirely escape being recognized as hereditary.

In summary, the problem of embryonic defect and death in the human species is much more complicated than was formerly supposed. It is clear that in man, as in other animals, genetic and constitutional factors are operative in some cases, disturbances of the maternal environment in others, in the production of prenatal damage and loss.

8

The investigation of disease by the physician-scientist is necessarily an impersonal affair, for judgment must be unhampered by the heartstrings and yet when all has been said that present knowledge permits about congenital abnormalities and prenatal death, one is sadly aware that many of these domestic frustrations we have tried so hard to understand are attended by bitter disappointment and a woman's tears and also that for the devout of Holy Church every death of an unborn infant implies eternal nonfulfillment of one more soul. I do not forget the child for whose salvation I fought, a heretic beside the faithful, long ago in the hospital of Saint Agnes. His father was waiting in the surgery corridor. I have no idea what the Sister said when she broke the news that both wife and infant were dead. Let us hope she extended the consolations of religion without the technicalities, and did not think it needful to remind him that his little son had died unbaptized. She was a kindly woman if she is living now, and remembers that particular baby, no doubt she imagines him as one of a throng of cherubs—or shall we say demi-cherubs?—wingless and unhalo'd, playing in a green field outside the gates of heaven not in torment, not even unhappy, but certainly very wristy.

ful because he is not permitted to walk hand in hand with his mother before the Throne of Grace. Had they lived, he would now be 32 years old. He could have attended the Seminary, and might ultimately have become an archbishop. A few minutes would have made all the difference.

As a matter of fact, his brief history is not, in its medical aspect, a very good illustration of this chapter, for the rare intra uterine accident that ended his earthly career is one of those we still do not in the least understand—there is no reason to think it hereditary and no proof that it has an environmental cause—but to me he will always represent the whole host of those who die before they are born, whether as eggs, as embryos, or as infants almost ripe for birth. To each of these, according to a dogma set forth by the Fathers, and poignantly cherished before most of the altars of Christendom, at the moment of conception an immortal soul is given—but if the small body is too frail to carry its burden until the time for baptism, it must relinquish it to eternal doom. Some theologians have thought, indeed, that lost souls of this class are condemned, like those of unshiven malefactors, to the extremest pains of hell, but St. Thomas Aquinas (as I have already mentioned) declares that their penalty is no more than perpetual exclusion from the sight of God. St. Augustine, and long after him the Calvinists, explained away the seeming injustice of such punishment of souls that never had a chance, by pointing out that we are all so steeped in original sin that no soul could reasonably hope to escape—we can only be thankful for the mercy by which some are spared.

The views of an embryologist on this subject may not be unanimously acceptable. It will be said that there are more things in heaven and earth than can be seen with a microscope. But I have been called to the rostrum and I shall state my opinion. The embryologist is keenly aware—who could know it better?—that the egg is endowed with the

marvelous gift of life, but he sees this as a general property of organic creatures and he would never have conceived the idea that an immaterial self-conscious existence, destined to endless bliss in heaven or the torments of the pit, is entrusted to the uncertain custody of the human egg. One human being survives a hundred years, another dies while still an individual cell. If it were true that every embryo is bearer from the first of an immortal soul, there could indeed be no escape from the doctrine of predestined damnation, for (as we have seen) a third, perhaps even a half, of all human embryos cease to live, many of them destroyed by predetermined factors, before they become accessible to baptism or whatever ritual observance may be thought to sway the balance of heaven and hell. Looking through the microscope at the physical structure of embryonic man, I see no heaven bound chariot of the soul, but only a frail congeries of animal cells, fraught indeed with promise beyond all other embryonic creatures but of necessity bound to grow and to organize itself as an animal if it is to be a man. Merely to watch that infinitesimal bit of living tissue acquire the bodily configuration of a human being is a great and marvelous privilege as King David sang at Jerusalem when he was meditating upon this same subject, "Such knowledge is too wonderful for me, it is high, I cannot attain unto it." How then shall I speak of the spirit? but humbly employing such vision as may be granted to an embrvologist, I declare my conviction that the spirit of man—all that makes him more than a beast and carries him onward with hope and sacrifice—comes not as a highborn tenant from afar but as a latent potentiality of the body. It too is received as a germ, an opportunity something to develop. The spirit, with the body, must grow and differentiate organizing its inner self as it grows, strengthening itself by contact with the world, winning its title to glory by struggle and achievement.

Regardless however of differing concepts of the soul, it is

true that to a certain extent the fate of the embryo is foreordained. Every individual carries with him from the fertilized egg a set of genes that guide and limit the resources he can set against his environment. An embryo that doubly inherits a lethal gene is absolutely predestined to brief and fruitless life and others, even though they happen not to suffer by inheritance, become the victims of a statistical if not an absolute foreordination, for some are sure to be stricken in utero by one kind of mischance or another. The study of prenatal defects, while abolishing superstition, has thus extended the known range of natural mortality and deepened the riddle of fate but does it not strengthen the call of duty and aspiration? Those of us who survive are truly the elect, chosen from a larger multitude. In this fact we may take a melancholy pride, like soldiers who close the ranks and march on when their companions fall. Let us make all we can of this life, we are fewer than we thought. When he who ponders these things cries that all flesh is grass, science joins with faith, replying Make green, then, in thy season, the place wherein thou growest.

III

THE GENERALITY AND THE PARTICULARITY OF MAN

I said in mine heart concerning the estate of the sons of men that they might see that they themselves are beasts.

Thou hast made him a little lower than the angels, and hast crowned him with glory and honour

1

I ONCE had a caller at my laboratory who spent an afternoon trying to demonstrate that the human race is the result of a cross, sometime in the dim past, between an angel and an anthropoid ape. This hypothesis, which bobs up repeatedly in visionary minds, rests upon a well-established and on the whole valuable trait of human nature, self-esteem. It has been all too clear, at every stage of history, that man is a beast, whether or not he also contains a dash of the angelic. Yet we are not willing to admit it. Every argument that poetry, religion, the intellect, or mere racial pride can supply is used to bolster our self asserted distinctiveness among living creatures. A man will work and pray and if necessary die for ideals which imply the claim of special rank for his own kind. Even those men of science who have tried without prejudice to determine the place of man in organic nature have most of them felt a certain restraint in classifying him as an animal.

Scientific thought on this subject began with the idea that man is a highly superior creature who happens to present certain resemblances to the animals. It has only very slowly proceeded to the view that he is an animal who happens to possess certain special abilities. Aristotle, for example, in his *History of Animals* placed man by himself

in an exclusive class of living things. He divided the animals somewhat vaguely into those which are bloodless (or as we should now say, the invertebrates), those which have blood (the vertebrates), and man. He said that the principal genera having blood are man, the viviparous quadrupeds, oviparous quadrupeds, birds, and fishes. Man's special powers of thought and action, however, seem to separate him too widely from the four footed animals to permit including him with them in one class. Some animals, he thought, share the properties of both man and the quadrupeds: these are the monkeys and baboons.

The view that man occupies a special position in nature fits in with an idea about the relationship of living things which was implicit in Aristotle's writings and which influenced the thought of zoologists until the 19th century. Indeed, it still underlies a good deal of casual thinking about the relative place of man and the animals. This is the concept that all animals and plants, in fact all natural objects, inorganic as well as organic, are arranged in a single series or scale of ascending rank, with man at the top. Such a view as this about the human species was well suited to the philosophy of the Middle Ages and the Renaissance, when the supreme value which Christianity set upon man's immortal soul strengthened the tendency to regard him as a very distinctive kind of being, occupying the chief place in earth's hierarchy. "Man, the most excellent and noble creature of the world," says Robert Burton in the *Anatomy of Melancholy*, "the principal and mighty work of God, wonder of nature, audacissimum naturae miraculum, the marvel of marvels, the abridgement and epitome of the world, sovereign lord of the earth, sole commander and governor of all the creatures in it, far surpassing all the rest, not in body only, but in soul."

Such a rhapsody, and indeed the whole proud assumption

that man is different to an immeasurable degree from other animals, might have been less confident, and the battle between science and orthodoxy over the question might have begun far earlier than the 19th century, if man had known anything about his higher simian relatives. Had the chimpanzee or gorilla been available for anatomical comparison, mankind would not have seemed so far in advance of his fellow creatures. Until the 17th century there were only vague stories about man like animals in distant Africa and Asia. The first of the great apes known to have been brought alive to Europe was a chimpanzee described in 1641 by Nicholas Tulp, the Dutch anatomist who is the leading figure in Rembrandt's painting "The Anatomy Lesson." The earliest recorded dissection of a great ape was reported in a remarkably accurate and sensible work by Edward Tyson, published by the Royal Society of London in 1699. Tyson made his opinion perfectly clear that the body of this animal—he too was studying, like Tulp, a young chimpanzee—resembled that of man far more closely, as he said, "than any of the ape kind, or any other animal in the world, that I know of." Evidently, then, man has closer relatives in the anatomical scale than had been realized before a fact which thenceforth had to be taken account of by those who undertook the classification of animals. Théophile Bonnet, for example, an industrious French naturalist of the 18th century, published a detailed tabulation of the Scale of Beings, beginning with Fire, Air, and Water through the ascending ranks of sulphurs, metals, stones, corals, molds, lichens, plants, the various invertebrate and vertebrate animals, upward to the quadrupeds, monkeys, chimpanzee, and man. All that such a list requires to make it reach from the lowest to the Highest, is to add the celestial hierarchy of angels, archangels, powers, and principalities. Man may thus be considered either the highest of beasts or the lowest

of the heavenly hosts, an arrangement which permits him to be dealt with by both biology and eschatology without conflict.

The idea of the Scale of Beings broke down, however, with the wider exploration of nature. As the naturalists built up an even larger list of species, it became absurd to try to rank them in serial order. Who shall say whether the fox is higher than the wolf, or a sparrow than a robin? After the appearance in 1735 of Linné's *System of Nature* the science of classification was revolutionized. The scalar arrangement gave way to the newer and more manageable method of classification by classes, orders, and families. Linné himself never saw one of the great apes, but Tyson's monograph had made it necessary for him to find a place for the chimpanzee which should not be very far from man, on one hand, or the monkeys on the other. He therefore defined seven orders of mammals, one of which he called¹ the *Primates*, comprising man, the apes and monkeys, the lemurs, and the bats. His reasons for grouping the bats so closely with the others need not concern us here, they were not valid, and later zoologists placed these creatures in a special order, the Chiroptera. Whether or not the lemurs are enough like the apes and monkeys to be placed in the same order with them is still actively debated. It is a question on which the embryologists have something to say and we shall return to it later.

Not all the competent zoologists after Linné were willing to follow his bold consideration of man as a member of the same order of mammals as the apes and monkeys. Johann Friedrich Blumenbach, the founder of physical anthropology, in his classification of 1779 placed man in a separate order which in a later work he called *Bimana*, two-handed, in contrast to the other apes and monkeys, the *Quadrumania*, four handed. Thomas Pennant, a good English natu-

1. In the 10th and later editions, 1758 ff.

ralist, in 1781 wrote, "I reject Linné's first division, which he calls Primates or Chiefs of Creation because my vanity will not suffer me to rank mankind with Apes, Monkeys, Maucaucos and Bats, the companions Linnaeus has allotted us even in his last system" Baron Cuvier's great *Règne Animal* of 1817 still maintained Blumenbach's special Order of Bimana, occupied solely by man in all his pride.

All this may seem a merely technical question, but the British American public of mid Victorian days did not think so. The outburst of an open controversy, about the year 1860, on the zoological position of man was surely one of the great turning points of human thought. My readers are all familiar with this episode and in particular with the part played in it by Thomas Henry Huxley. By the time Huxley had finished his debates with Bishop Wilberforce and Professor Owen the attitude of every educated person respecting our place in nature was permanently affected. No philosophy of life, no system of ethics could any longer neglect the animal nature of man. Three circumstances brought the question to a head. One was the progress of geographic exploration, through which knowledge of the great apes came flooding into the zoological gardens, museums, and dissecting rooms of Europe and America. Travellers in eastern Asia and Africa sent home specimens of the chimpanzee, gorilla, and orang utan. Richard Owen, the great comparative anatomist at the Royal College of Surgeons of London and afterward at the British Museum was thus enabled to give a comprehensive description of the skeletons of the chimpanzee and orang utan in 1835. An American medical missionary, Thomas S. Savage, collected skeletons of the gorilla in 1847 from which Jeffries Wyman of Harvard worked out the osteology of that species. The gibbons, smallest of the man like apes, and known in the 17th century only from one specimen described by Buffon, were also made the subjects of anatomical investi-

gation. Thus it became well understood that there are five genera of anthropoid apes, forming a group clearly distinguishable from the monkeys, and in some characteristics more like man.

Another factor was the discovery of remains of fossil men, especially the sensational find at Neanderthal in 1857, which proved the existence in prehistoric times of a now extinct species of man of coarser build and lower brow than modern man. Thus it appeared that the gap between man and the monkeys was being filled from both ends.

The third reason for the sudden importance of the question of man's zoological position was the announcement by Darwin and Wallace in 1858 of the theory of evolution by natural selection. Mere anatomical facts, or even the discovery of fossil man, might have attracted little immediate attention outside the laboratories and museums, but the publication of Darwin's *Origin of Species* made a public furore. Its implication that the human species is descended from an ape-like ancestor was attacked on grounds both of religion and of science. Some conservatively minded anatomists came to the front with observations that seemed to prove wide differences between the anatomy of man and that of the great apes. Richard Owen in particular had long since described supposedly fundamental divergencies between the skulls and brains of man and of the great apes, thus apparently confirming the classification of his teacher Cuvier, by which man was set apart as the only species and genus of the Order Bimana. This anatomical observation, now brought forward in opposition to the Darwinian hypothesis, was answered fully and devastatingly by Huxley, together with other arguments, in *Man's Place in Nature* (1863), one of the masterpieces of scientific exposition in English, in which he showed that in many anatomical fea-

tures the differences between man and the great apes are actually less than those existing between these apes and the monkeys.

In spite of all that he did to emphasize the distinctive features of the great apes² as contrasted with the monkeys, Huxley did not set them up in his classification as a separate suborder or even as a separate family. In his *Anatomy of Vertebrated Animals* (1872) he ranked the primates as shown below. It will be seen that he gave man much the same relatively distinctive position as had Linnaé.

Order	Suborder	Family	Subfamily
	Lemuridae (lemurs)		
		Aretopithecini (marmosets)	
PRIMATES	Simiadæ	Platyrrhini (New World monkeys)	
		Catarrhini (Old World forms)	Cynomorpha (Old World monkeys)
			Anthropomorpha (anthropoid apes)
	Anthropidae (man)		

It remained for Sir William Henry Flower to grant (1883) full recognition to the anthropoid apes as a group so similar to one another, and so different from the monkeys, that they must be placed on the same level of classification with the Old World monkeys. Thus as increasing in

2. For the sake of clarity the term *anthropoid apes* is used in this book to include the gibbon, siamang orang-utan, gorilla, and chimpanzee; *great apes* means only the last three.

formation has been obtained about the primates, the anatomists have gradually elevated the anthropoid apes to a higher level of classification, at the same time ranking the human species more and more intimately with the other animals of similar type. In Aristotle's time man was set apart from all the other vertebrates. Linné included him with them and grouped him with the primates, but in a separate suborder as we should now say, Huxley set forth the claim of the great apes as his near relatives, and 20th-century biology, rich in knowledge of primate species, considers living and fossil man as only one family among four which form the tribe of Old World apes and monkeys, thus

Infraorder Catarrhini

Family Cercopithecidae (Old World monkeys)

Family Hylobatidae (gibbon, siamang)

Family Pongidae (orang utan, gorilla, chimpanzee)

Family Hominidae (man, living and fossil)

If this slow but steady demotion of man (as judged by the biologists) were to continue, the next step would obviously be to throw over the last quantum of human pride and classify our species merely as one of the subfamilies of the catarrhine apes in other words to say that we are simply one particular kind of ape or monkey. There are at this moment biologists who would do just that, but the differences and resemblances upon which such a decision must be based are so diverse that it becomes a matter of private judgment, hardly subject as yet to general agreement, whether to place the human species with the great apes or with the monkeys.

Punch's famous query, made at the height of the Huxley Owen controversy in 1861, quite literally expresses (excepting the first line) the question now awaiting the answer of science

Am I satyr or man?
Pray tell me who can,
And settle my place in the scale
A man in ape's shape,
An anthropoid ape,
Or a monkey deprived of a tail?

The majority of investigators, however, still think that man is sufficiently distinctive to constitute a family by himself. After all, if he is an ape he is the only ape that is debating what kind of ape he is.

2

What evidence has embryology to bring to bear upon this great problem? In answering this query we must first consider briefly the way in which biologists proceed to work out the classifications and tables of relationships we are talking about.

Whether from practical need or plain curiosity, people have always felt a strong wish to classify living creatures. Nature seems a vast complexity. We crave some knowledge of its organization. The earliest written classification of animals appears in the ancient book of Leviticus, wherein the children of Israel were taught to discriminate between those beasts that both part the hoof and chew the cud, and those which possess only one of these characteristics, or neither; and between those creatures of the sea which have and have not fins and scales. Aristotle went a good deal farther, by suggesting a much larger list of distinguishing features, many of which have been used by science ever since, such as differences in teeth and tusks, hide and hair, nails and claws, and in the mode of reproduction, i.e., viviparity contrasted with egg laying. Beginning with the work of John Ray (1693) we see the development of a thorough

going tabular classification in which the plants and animals were listed and grouped in a systematic way according to their various characteristics, just as a collection of postage stamps is arranged by country of issue, date of issue, monetary denomination, and minor varieties of color, perforation, and cancellation. The ordering of living things is much more difficult, however unlike postage stamps, information about the date of appearance and the place of origin is unavailable there are more characteristics to be considered there are confusing intermediate forms between the classes, animals are more variable individually than stamps and can change their appearance and even their anatomy as they grow Each biologist who has had a try at the perplexing task of classification naturally had his own idea as to which characters are more important for the purpose. Some decided chiefly by the type of foot and others by the teeth Men like Ray and Linné showed their *genius* by noting a wide variety of characters and then choosing the more significant as the basis for discrimination. Linné, for example, perceived that the possession of mammary glands and the secretion of milk is a fundamentally significant character He set up a class of animals on that basis, calling them *Mammalia*. He had the courage to put the whales in this class in spite of the fact that their superficial resemblance to fishes had baffled all the previous systematizers.

Linné's method of dividing the mammals is well illustrated by his definition of the Order of Primates, which I cite in slightly simplified terminology

"Inferior front teeth four, parallel, canine teeth solitary (a single pair above and below) Mammary glands in the pectoral region, one pair The anterior extremities are hands. The arms separated by collar-bones, the gait usually on all fours They climb trees and pluck fruits." A list of animals made up in this way is primarily a key for identification, like those which are nowadays used by nature lovers who want to recognize birds or wild flowers by spot

ting distinctive combinations of traits. It implies no statement of family relationship, though of course the method often results in bringing together natural groups. On the other hand it may be misleading by emphasizing easily observed but superficial characters while neglecting fundamental similarities that can only be detected by laborious dissection.

In the late 18th and the 19th century, however, when the concept of organic evolution began to be considered seriously, the ancestral history of the various kinds of plants and animals began to be sought out, and classification inevitably tended to follow the presumed lines of descent. To cite an example close to our present interest, the biologist who decides that the tribes of Old World monkeys and great apes respectively are to be considered two families of an infraorder called Catarrhini, does not mean merely that they are much alike in appearance and anatomy; he intends to say that in his opinion the two families are related by descent, having evolved from a common ancestor. If he enrolls the genera of man living and fossil, as another family of the Catarrhini, he implies that man also shares the common ancestry. If he is one of those who thinks the relationship is even closer, he will place the human genera within one of the other families according to his best judgment. There are of course many gaps in our knowledge of these relationships; it is often impossible to settle the probable line of descent. The best that can then be done is to list the animals on the basis of anatomical classification, and leave it to anyone who wishes to draw up and prove, if he can, his own idea of the "family tree."

The judgments of the classifier are largely based upon a consideration of the structure of the living and fossil forms, controlled to some extent by knowledge of the functional activities of the organisms. The great divisions are determined by fundamental differences which are usually quite obvious. Everyone can appreciate the grand division into

Invertebrates and Vertebrates Subdivision of the Vertebrates into classes involves a somewhat more technical judgment. At present seven chief classes are recognized, as follows

- I. Agnatha (jawless vertebrates, e.g., lamprey)
- II. Chondrichthyes (cartilaginous fishes, e.g., sharks)
- III. Osteichthyes (bony fishes)
- IV. Amphibia (e.g., salamanders, newts, frogs)
- V. Reptilia (e.g., turtles, lizards, snakes, alligators)
- VI. Aves (birds)
- VII. Mammalia

Most of these groups are recognizable without difficulty. Anyone can distinguish a mammal, a bird, and a fish, in spite of a few confusing instances such as the resemblance of bats to birds and of whales to fishes. Distinction of reptiles from amphibians, however, requires good observation of their respective anatomy and breeding habits. Separation of the cartilaginous from the bony fishes and the judgment that they belong in separate classes require special knowledge acquired by dissection.

Limiting our attention to the Class of Mammals, three subclasses are recognized

1. Prototheria (monotremes or egg laying mammals, e.g., duck bill platypus)
2. Metatheria (marsupials, e.g., opossum, kangaroo)
3. Eutheria (placental mammals)

Here, it will be noted, the primary division depends upon the method of reproduction. All these animals have mammary glands and feed their infants on milk, but they differ in the method of incubating their young, whether in nests, or in brood pouches after short residence in a uterus, or by full uterine gestation. There are also fundamental anatomical differences between the three subclasses, readily discernible.

ible by a careful dissector. The reproductive organs are of course very unlike, but besides this there are differences in details of bones, muscles, nerves, teeth, and viscera.

A currently accepted classification of the Eutherian mammals sets up eleven chief orders:

- a. Insectivora (e.g., moles, shrews)
- b. Carnivora (e.g., cats, dogs, weasels, bears)
- c. Perissodactyla (odd-toed hoofed animals, e.g., horses, tapirs, rhinoceros)
- d. Artiodactyla (even-toed hoofed animals, e.g., pigs, camels, deer, oxen)
- e. Proboscidea (elephants)
- f. Rodentia (e.g., beaver, squirrel, mouse, rat, porcupine, guinea pig)
- g. Lagomorpha (rabbits, hares)
- h. Chiroptera (bats)
- i. Cetacea (whales)
- j. Edentata (e.g., armadillos, sloths)
- k. Primates

Again, the characteristics which define these orders are partly obvious, for example, those of the bats and the elephants, and partly so technical as to require expert anatomical knowledge to recognize them. The tabulation of course depends upon the opinion of the classifier—many zoologists for example put the rabbits and hares not in a separate order of their own but in a suborder of the Rodentia. Having adopted some such list, the comparative anatomist if he is interested in evolution then proceeds to compare the resemblances and differences between the orders in the hope of working out a plausible scheme of lines of descent.

A fanciful illustration may help to explain his task (Fig. 14). Imagine an investigator who tries to work out the phylogeny of gasoline-propelled vehicles, knowing only

GENERALIZED

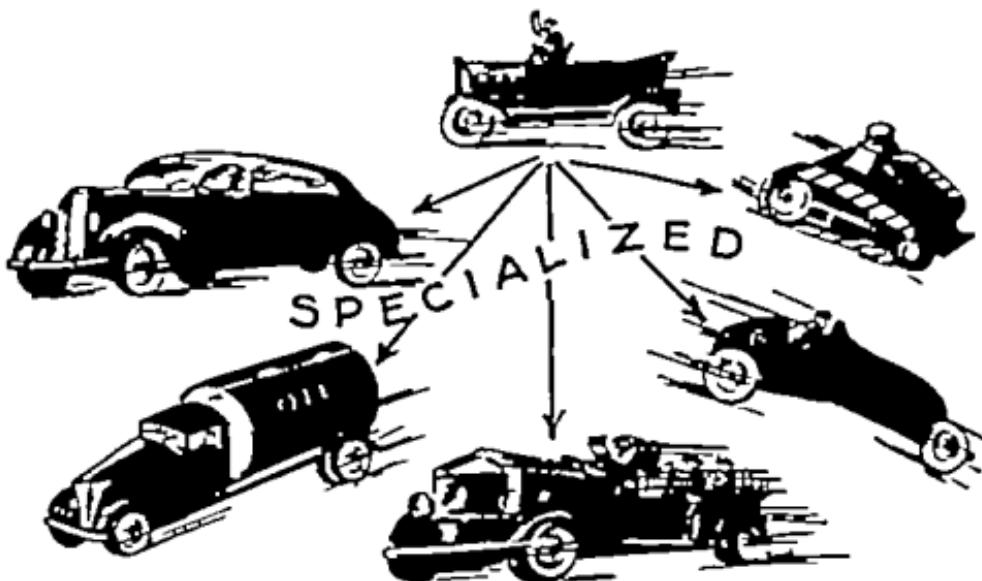


Fig. 14 Generalized and specialised automobiles.

those he sees in the roads and the junk yards. Inspecting such diverse machines as a racing car, an oil truck, a fire engine, and an armored military tank, he sees clearly that these are late, specialized developments from some simpler type. Each of them, however, has a chassis and an engine. Most of them have four wheels. These must be the fundamental characteristics; such things as oil tanks, fire ladders, and cannon on the other hand are special adaptive features, by no means common to all kinds of automobiles. On the whole, a de luxe passenger car is less specialized than the foregoing types, but even it has a number of adaptive features such as opera seats and a radio. Our hypothetical investigator would see that the best clue to the ancestral motor car is given by an old roadster of a so-called "popular make." In the biological sense of the words, it is a primitive or generalized type.

A shrewd thinker in this imaginary branch of science might go farther and try to reconstruct mentally the ex-

tinct ancestor of the most nearly primitive cars of the present day. He might plausibly guess, for instance, that pneumatic tires represent an evolutionary improvement, and that they were preceded by solid rims but knowing what primitive roadbeds were like, he would suppose that the rubberless wheels were larger than those of today, and the car higher-slung. The engine was probably less efficient than nowadays the car must therefore have been lighter. Before that there was probably no engine at all. Thus he forms the hypothesis that the modern motor car is descended from a light, high wheeled, buggy like horse-drawn carriage.

If our theorizer happened to observe one of the sea going trucks now being used by the army, he would at first be puzzled. The thing looks as if it is some sort of modified motor launch, in the line of descent from a primitive canoe but dissection shows that it has the skeleton and viscera of an automobile. Its boat like form is merely an instance of "convergent evolution" like that by which the whales, though they descended from land mammals, have acquired an external resemblance to the fishes. Studying a steam roller, the investigator would realize from its form and its internal anatomy that in spite of its habit of self propulsion on ordinary roadways like gasoline cars, it represents a different line of descent, namely through the railway locomotive, an order of vehicles which diverged from the primitive ancestral wheeled cart a long time ago.

Similar mental operations guide the zoologist in his effort to deduce from the structure of living and fossil animals the lines of descent by which they each evolved from more primitive creatures. His task is very difficult, because the animal forms are vastly more numerous, more varied, and more complex than the forms of motor cars. He has to learn to see small but important clues while ruling out merely superficial resemblances, and to weigh the mass of the evidence rather than be swayed by a few striking de-

tails. The amount of minutiae which must be considered is incredible. In citing here a currently acceptable family tree of the mammals, I must content myself with giving the result, without attempting to outline even a small part of the evidence. The following diagram (Fig. 15) has been taken, with considerable simplification and some modification, from *The Orders of Mammals* by W. K. Gregory (1910).

It will be noted that as seen by the experienced mammalogist, the anatomy of the primates suggests that they occupy a stem of the diagram along with the bats and the insectivores. Our common ancestor was probably a small, sharp-eyed, quick moving, furry animal living in the trees.

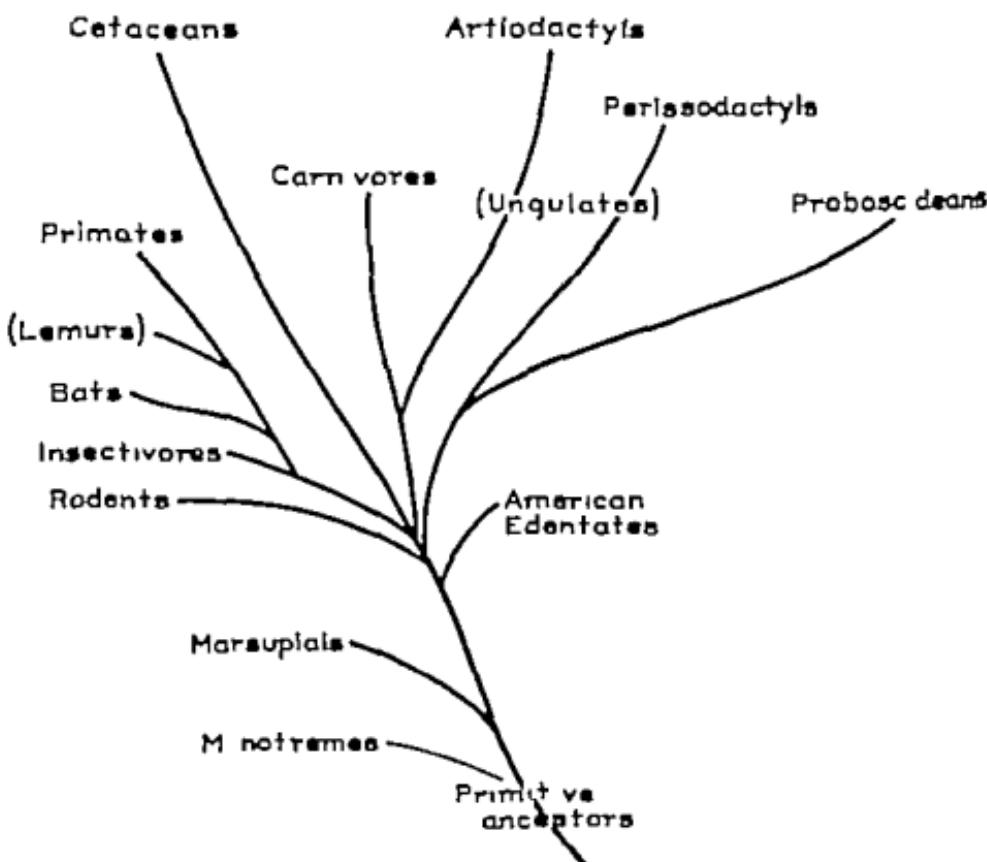


FIG. 15. A hypothetical family tree of the mammals, modified and simplified from W. K. Gregory *The Orders of Mammals* 1910.

8

It is generally supposed, by students of the anatomy of living and fossil primates, that back in the earliest, or Paleocene, epoch of the Tertiary period of geologic time, perhaps fifty million years ago, one of the tree-dwelling insectivore-like species then living evolved into the ancestral line of present-day primates. Fossil primates are scarce, and the exact nature of the earlier forms is uncertain, but if this hypothesis of their origin is correct, the line soon gave rise to an offshoot which was ancestral to the lemurs, those small four-footed animals, something like squirrels in general appearance, whose present-day representatives are found mostly in Madagascar. As we shall see later, a few biologists doubt the correctness of including the lemurs among the primates, even as a side branch. All lines of evidence agree, however, in admitting the queer looking, pie-eyed little tarsier (technical name, *Tarsius*) of the East Indies to a place close to the stem of the primate family tree. This species has a relatively large brain and eyes which look forward, converging sufficiently to indicate that it has stereoscopic vision. The muzzle is shorter than that of the lemurs, suggesting the simian human type of face. *Tarsius* itself has striking specializations, including particularly a set of large pads on the toes which it uses in clinging to trees, and an extremely long ankle, whence its name; but there are numerous fossil tarsioids of more generalized character which lived in Eocene times, among which, it is thought, was the progenitor of later monkey-like forms.

Next, presumably, the flat nosed (Platyrrhine) monkeys, of which the now living examples are found only in tropical America, evolved somewhat divergently from the main line of descent. In the shape of the nose, in the dental formula (three premolar teeth in the lower and upper jaws on each side), and in various specializations possessed by

many of them, such as the prehensile tail, the American monkeys are clearly different from the Old World forms. This leaves three kinds of primates still to be classified, namely the Old World monkeys, the anthropoid apes, and man. Everyday observation, of the sort anybody can make in the zoo, agrees with the results of detailed scientific study in associating these three groups together. They all have quite large brains, the premolar teeth are in all of them reduced to two on each side of each jaw. The thumbs are opposable, i.e., can be bent against the palms and other fingers, and so are the great toes, except in man, who has lost that particular trait.

We need not devote much space here to the detailed specifications by which the three kinds of catarrhine primates are distinguished from each other. Man and the anthropoid apes have chests which are broad from side to side and shallow from back to breastbone, unlike the monkeys, which have narrow deep chests like other mammals. Man and the anthropoid apes tend to have an erect or semierect posture, and they all lack tails. The fact is, however, that as we approach the terminal branches of the family tree of the mammals it becomes harder and harder to define the differences in logical, scientific, exception proof terms. Every body can tell a bear from a raccoon offhand but those who have seen the recently publicized giant panda in a zoo would find it difficult to state categorically the characters by which they would decide whether to assign that species to the bear family or to the raccoon family. The expert does it by comparing details of structure in the teeth, skull and limb-skeleton, and viscera which he knows are characteristic of the undoubtedly bears and raccoons respectively.

Difficulties of much the same sort have made the precise relation of man to the Old World monkeys and apes a problem as obscure as it is fascinating. The question arose as soon as people were first willing to admit the probable blood

relationship at all, and it is just as good for a debate now as it was in Huxley's time. I have already referred to the fact that there is not even full agreement at the present time as to whether man (living and fossil) is to be given standing as a separate family or placed within that of the great apes or perhaps that of the Old World monkeys. Conservative opinion, based upon study of comparative anatomy of all the living forms and the fossil apes, now draws up the classification more or less as follows:

Order PRIMATES

Suborder Lemuroidea

Suborder Tarsioidae

Suborder Pithecoidea (or Simiac)

Infraorder Platyrrhini (American monkeys)

Family Hapalidae

Family Cebidae

Infraorder Catarrhini (Old World forms)

Family Cercopithecidae (macaques, langurs, baboons, etc.)

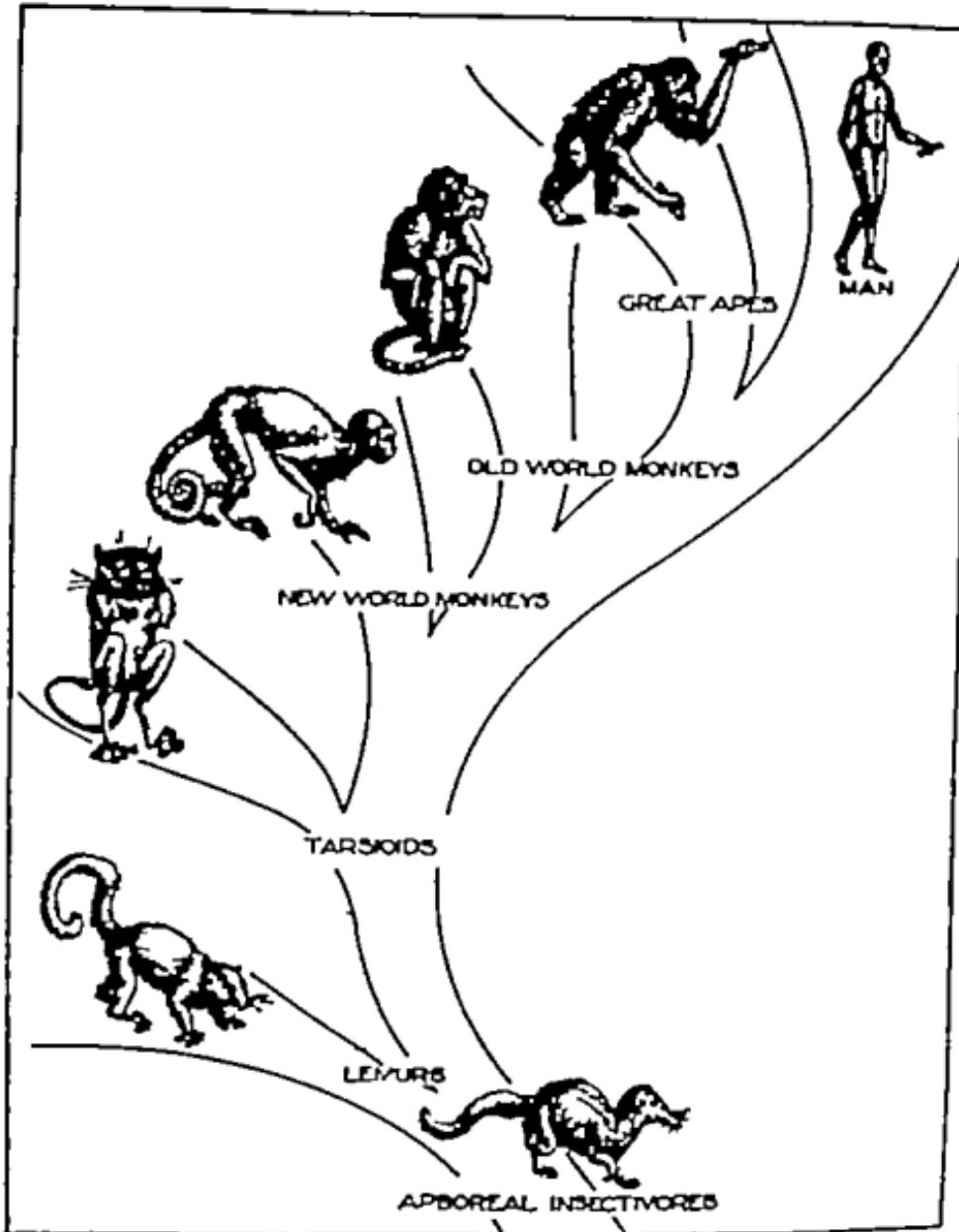
Family Hylobatidae (gibbons and siamang)

Family Pongidae (orang utan, gorilla, chimpanzee)

Family Hominidae (man)

This is the stamp-album kind of tabulation. A family tree representing the same body of opinion and evidence is shown in Professor Romer's simplified pictorial diagram reproduced herewith (Fig. 16). It differs from the above classification only in condensing the gibbons and the other anthropoid apes onto one twig of the tree.

This diagram represents the commonly held view that man is closer to the great apes than to the monkeys. Not only is this the opinion of many scientists but it seems also to be tacitly held by the public, for visitors to zoos are always particularly interested in the chimpanzees, gorillas



Fm. 16. A simplified family tree of the primates. From A. S. Romer *Men and the Vertebrates* by arrangement with the University of Chicago Press.

and orang utans. The large size of these animals, their large crania, their taillessness, and their more or less man like posture and behavior seem to suggest a kinship outranking

that of the smaller primates. Most of the scientific leaders who took part in the debates of the 1860's and 70's, including Darwin, Huxley, and Haeckel, agreed with this opinion, on the evidence of the anatomy as they saw it. They assuredly did not think that one of the existent kinds of great apes was the direct ancestor of man but they believed that all these creatures and man had a common ancestry, and that the progenitor of primitive man was an animal of much the same sort as the great apes. Darwin said this explicitly in *The Descent of Man*. Huxley's famous group of popular lectures, *Man's Place in Nature*, is devoted to the same thesis. There were, however, able contemporaries who were not convinced. A brilliant little book, *Man and Apes*, published in 1874 by St. George Mivart, took issue with Darwin and Huxley. Mivart, an excellent comparative anatomist, adopted a method begun by Tyson and used frequently since in connection with this problem, of listing one by one the anatomical characteristics of the animal under discussion, to see how the resemblances and differences are distributed among the various families and species. He agreed that in the structure of the brain the great apes approach man more closely than do the monkeys. This is true also, he thought, of the muscular system. On the other hand, said Mivart, all the great apes have strongly projecting canine teeth, whereas the human canines are not very prominent; this human characteristic is also possessed by the lemurs. A true vermiform appendix is present only in anthropoids, but is most like that of man in the gibbons, not in chimpanzee or gorilla. Mivart was able to list nine more or less important details of anatomy and bodily proportions in which the baboons excel all the great apes in resemblance to man, and sixteen in which the admittedly remote South American monkeys come closest to man of all the primates. The whole of Mivart's argument should be read, to do him justice; he did not reject the evolution of

the human body, but he concluded that man has no special or exclusive affinity to any one kind of ape. In short, if he had made a diagram of the family tree he would have shown the human species branching from the stem as early as any of the monkeys.

This problem is so important that many competent people have worked at it, with the aid of a constantly growing body of information. Opinion has gone on swinging back and forth. Various extreme hypotheses have been put forward—two or three workers, for example, have seen so many points of resemblance between man and the gibbons as to suggest that these two kinds of animals diverged together from the common stock, before the separation of the line of the present-day great apes. On the other hand, the able contemporary English anatomist F. Wood Jones has been so much impressed by the relatively generalized structure of the human body (a subject of great interest to which I shall return later) that he has excluded all the monkeys and apes from the ancestry of man because their lines seem too much specialized, and has proposed that the human species diverged from the main primate stem a very long time ago, along with the tarsioids. Any reader who wishes to follow up this brief statement by wider and more technical reading, will be entertained as well as instructed by reading *Arboreal Man* by Wood Jones and then an all-star discussion by British scientists on the zoological position and affinities of *Tarsius*, published in the *Proceedings of the Zoological Society of London* in 1920.

The majority, however, of the workers who have expressed themselves on the subject in the last twenty-five years, trying to evaluate the degree of resemblance between the various primates, have upheld the original supposition that places man closer to the great apes than to the other primates, although there is considerable difference of opinion as to the degree of difference, or as to the period of

geologic time when the separation took place, which amounts to the same thing. Some (e.g., the late Sir Grafton Elliot Smith) thought that man, gorilla, and chimpanzee had a common ancestry as late as the Miocene period. W. K. Gregory, of Columbia University, lectured eloquently in London in 1934 in favor of the close relation of man and the anthropoid apes. An exceedingly careful reexamination of the question was published in 1936 by Adolph H. Schultz, of Johns Hopkins University, an experienced anthropologist who made a tabulation of the relevant anatomical features, taking account of quantitative differences on the basis of extensive measurements. The general result is shown in the accompanying diagram (Fig. 17). Schultz finds in the first place that the Old World monkeys (such as macaques, langurs, baboons) must have diverged first, leaving a common ancestral stem for the anthropoid apes and man, from which the gibbons soon diverged and then man. The remaining stem was that which gave rise to the present-day gorilla, chimpanzee, and orang-utan. An important feature of this conclusion is the very early separation of the human line from that of the great apes—in other words, Schultz (like several earlier 20th-century anatomists) finds enough resemblance to conclude that all these species had a common ancestry, and at the same time enough differences to make it appear that the human line has been evolving independently for a long time. This is about the average of the opinions expressed by expert workers in recent years. W. L. Straus, Jr., of Johns Hopkins University, a colleague of Dr. Schultz, places the separation of the human line somewhat earlier, though not as early as Wood Jones or Mivart would have it. Dr. Straus has made careful studies of the pelvis, the muscles of the extremities including the hand and foot, and the form and arrangement of the thoracic and abdominal viscera. One of his most important findings is that the form and use of the human arm

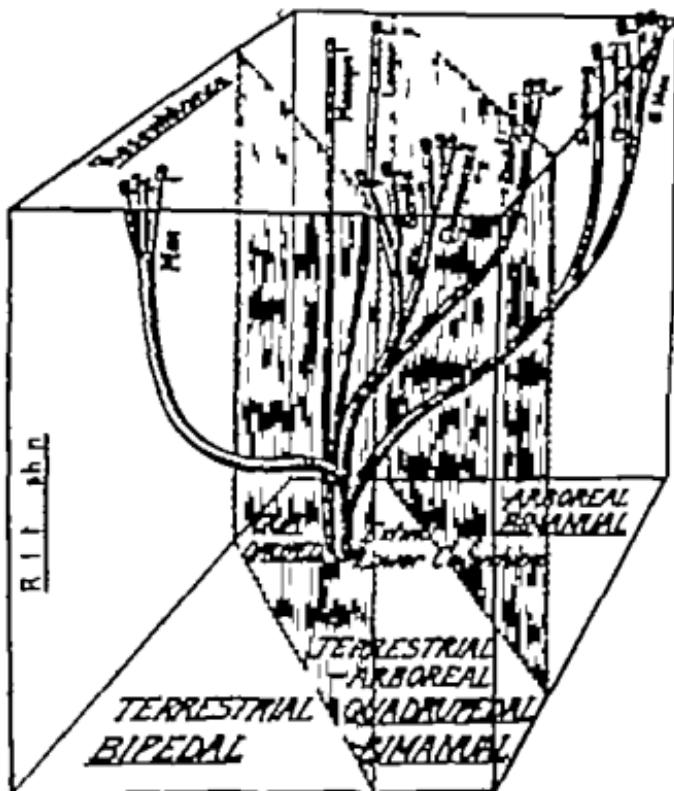


FIG. 17 Hypothetical pedigree of the recent catarrhine primates, by A. H. Schultz, based on his own studies. From *Quarterly Review of Biology* by courtesy of the Williams and Wilkins Company

and especially of the human hand make it improbable that man ever passed through a period when he traveled by swinging from his hands ("brachiation") as do the anthropoid apes. This fact, together with the large number of traits in which man approaches or resembles the monkeys, leads Straus to the hypothesis that the stem of the human species diverged from the general primate line when the ancestral creature had attained a structure something between that of the monkey line and that of the gibbons. He thus classifies man as more distinct from the great apes than does Schultz, and closer to the monkeys. Either of these conclusions agrees very well with the trend of research on fossil man, which suggests (as far as the small amount of available evidence goes) that the human species has been ana-

tomically distinct as long as have the great apes, and also with archeological research, which tends to set the origin of human cultural activities earlier and earlier in the past. Perhaps such conclusions will soothe to some degree the feelings of those who are unhappy about the animal descent of man, if indeed there are any still unreconciled to the idea of evolution.

The evidence considered up to this point has been almost exclusively anatomical. It should be added that the British writer Zuckerman has compiled (1933) what is known about differences in the functional activities of the primates, including such characteristics as control of the facial musculature, diurnal vision, stereoscopic vision, discrimination of colors, blood groups, types of breeding season, and the occurrence or nonoccurrence of menstrual cycles. Dr C. G. Hartman in 1939 added a few more items to the list. The sum of all this evidence clearly agrees with the general classification of the primates cited above as currently accepted, making man seem more like the great apes than the Old World monkeys. There are still fewer resemblances, in respect to these functional activities and characteristics, to the platyrhine monkeys and fewer yet to *Tarsius* and the lemurs. This analysis does not, however show a strongly marked resemblance of man to any one of the great apes more than another and thus it confirms or at least does not disagree with the conclusion already reached by the comparative anatomists, and supported by such distinguished students of fossil apes and men as Henry Fairfield Osborn and Sir Arthur Keith, that the line of man became independent in the Oligocene epoch perhaps forty million years ago.

The task of comparing one kind of animal with another in order to work out their relationship, is so intricate, so full of difficulties, that every scrap of available information

must be used. I have spoken thus far chiefly of the evidence from comparative anatomy of the adult animal, and from physiological and biochemical comparisons. To these the embryologist can add a wealth of additional information. It has already been pointed out that the embryos of various species of mammals can be distinguished from one another by the expert observer, all the way back to the stages of the one-celled ovum, and that there is an endless variety in the manner of implantation, in the arrangement of the embryonic membranes, and in the structure of the placenta. Is it too much to hope that by careful comparison and codification of these differences a flood of light may be thrown upon the problem of human descent?

In the first flush of enthusiasm over their discoveries of the early 19th century, embryologists seemed indeed ready to solve all the tangled questions of evolution, if only they could apply their methods to the whole animal kingdom. Von Baer, the man of genius who in 1827 discovered the eggs of mammals, made it his business to collect the embryos of all sorts of vertebrates and invertebrates. He perceived that an early embryo shows the general characteristics of the big group to which it belongs, before it acquires the special characters of its genus or species. A good example of this is seen in the fore-limb buds of birds and mammals, which are very much alike when they first grow out of the trunk. It is only later that they are distinguishable as wings or legs respectively. To cite a more general example already referred to in Chapter I, all the many-celled animals begin as a single cell, and practically all of them, vertebrates and invertebrates alike, go through a morula stage and then a blastocyst stage or something much like it, before they develop the particular characteristics of their own kind. Thus animals of higher and lower forms resemble each other much more when they are embryos than when they are adults. This is another way of saying that they all

start out more or less alike and diverge as they grow. It follows that the adults of lower, less differentiated forms which do not get very far from the embryonic, generalized type will to some degree resemble the embryos of higher, more divergent forms.

In the hands of Haeckel, whose facile writings had a great influence on popular thought about evolution in the latter half of the last century, these principles of von Baer were built into the so-called "biogenetic law" or theory of recapitulation, which declared that higher animals, in their embryonic stages, undergo the same series of transformations through which their ancestors passed during the evolution of the species. Mammalian embryos, for example, were thought to exhibit a fish stage and an amphibian stage, and Haeckel at one time went so far as to draw up a table of the progenitors of man which consisted, practically speaking, of a list of adult forms of now-existent types, all the way up from the invertebrates : e., segmented worm, cyclostome (lamprey), shark, bony fish, amphibian, marsupial, lemur, monkey, and ape. If such an idea were true in detail, the embryologist could solve all the relationships of the animal kingdom by studying the development of each species to see what kinds of animals their embryos successively resembled, but even those who cherished the notion most warmly had to agree that in the development of an embryo many stages of evolutionary history are omitted or greatly condensed. The human embryo is never a monkey or a reptile, nor is it ever like an adult fish or amphibian. It does, however, show remarkable resemblances to *embryonic fishes* and *amphibians*. A mere hint of this is shown in Plate IV, D and E—microscopic study of the internal organs as depicted in any textbook of vertebrate embryology gives convincing evidence of the fact. Yet such is the persistence of theoretical ideas that to this day some of the visitors to an embryological laboratory are actually disappointed to

find that human embryos are not sufficiently like adult fish to exhibit fully formed gill slits, to say nothing of fins and scales.

Comparative embryology of the more cautious variety has, of course, made great discoveries with respect to evolutionary relationships. One of its most spectacular achievements was Kovalevsky's revelation that the tunicates or sea squirts, lowly sessile dwellers on rocks and wharf piles, are in fact related to the vertebrates because their free-swimming embryos exhibit definite resemblances to the larvae of fish and amphibians. Another example is the way in which embryologists confirmed the distinction between amphibians and reptiles, already made with some difficulty by comparative anatomists, by showing that the embryos of the reptiles possess an amniotic envelope, which is not the case in amphibians.

To summarize, embryology can extend the range of comparative anatomy and comparative physiology by contributing evidence from the earliest stages of life, and especially by bringing forward for study an additional set of organs, namely the embryonic membranes and the placenta, which represent evolutionary adaptations of a most important kind. The findings of this branch of science, interpreted with wisdom, can aid in solving problems which no one branch of biology can deal with alone.

5

Let us see then what the embryologist can contribute toward understanding the position of man among the animals. I anticipated this question in §§5 and 10 of Chapter I, by citing evidence that places our species quite definitely among the primates. It was shown, for example, that differences in the placenta of various animals are highly significant. That organ in its gross form may be either diffuse, cotyledonary, zonary, discoidal, doubly discoidal, or some

other intermediate or variant shape (Fig 11). In its general structure it may be of the diffusely apposed type, or labyrinthine, or villous (Fig 18). In detailed microscopical structure, as pointed out in Chapter I, §10 (see Fig 12), the placenta exhibits four general types according to the

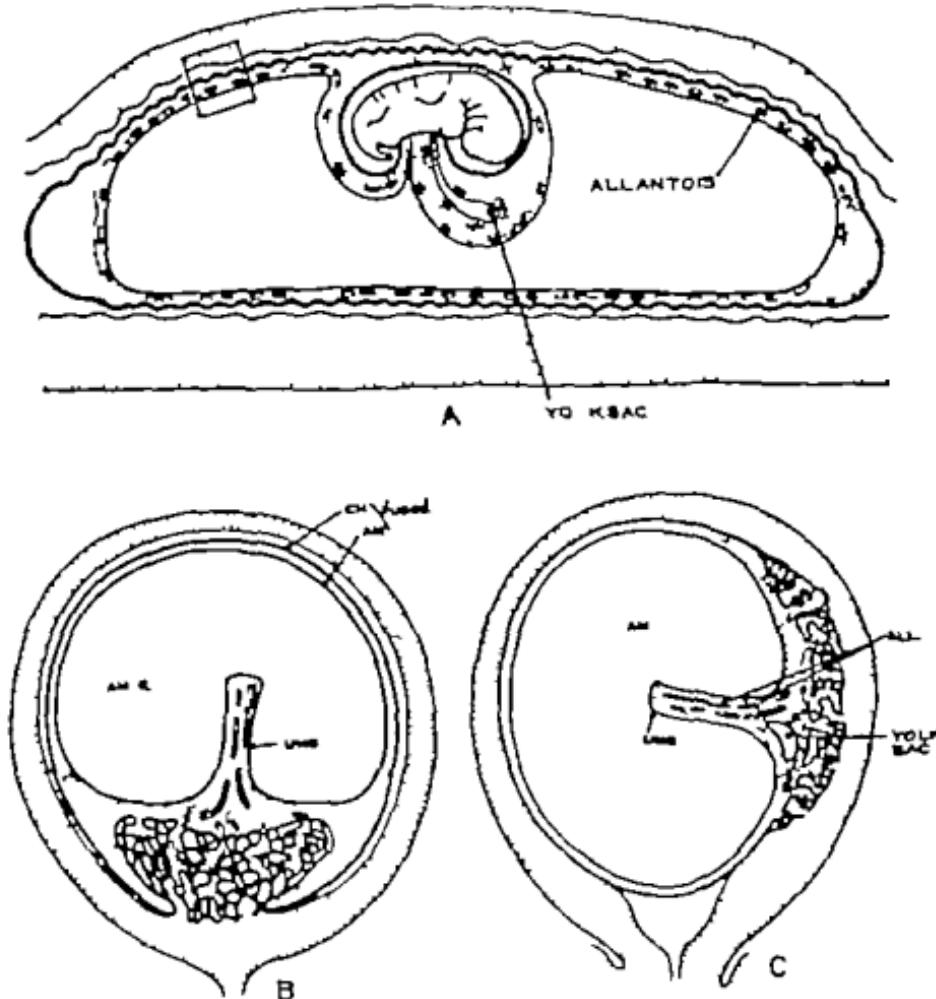


FIG. 18. Diagrams illustrating types of placentas. A, diffuse placenta (pig) showing simple apposition of chorion to lining of uterus. The rectangle serves to locate the area shown in Fig. 12, A. B, labyrinthine mesh of chorionic tissue interlocked with maternal tissue (Tarsius). C, villous placenta (human) much simplified. From *Carnegie Contributions to Embryology* by courtesy of H. W. Moesman.

number of cell layers which remain interposed between the blood streams of mother and fetus. The placenta has therefore long been subjected to careful study with the aim of comparing one species with another. Before the rise of microscopic anatomy in the 19th century there had already been attempts to use the gross form of the placenta as a guide to classification. This, as it turned out, was not a very useful method, because the comparison of gross form does not yield clearly separable groups, many rodents, for instance, have discoidal placentas as do many primates and various members of other orders. Microscopic analysis is much more helpful, as we shall see. The whole subject has been expertly discussed in two fairly recent papers, one of them by George B. Wislocki of Harvard Medical School (1929), the other the Croonian Lecture by J. P. Hill of London, published in 1932.* To make a long story short, it may be said in the first place that all the primates, except the lemurs, have discoidal or doubly discoidal placentas of hemochorionic type. Speaking only of the Old World forms, the shape of the placenta in the Cercopithecidae (macaques, langurs, etc.) is usually doubly discoidal, the baboons, in which it is singly discoidal, are an exception. In the Hylobatidae, Pongidae, and Hominidae (anthropoid apes and man) it is always singly discoidal. With respect to the arrangement of its internal structure, the placenta varies in a strikingly systematic way from *Tarsius* through the New World monkeys and Old World monkeys to the anthropoid apes and man. In the earlier-named of this series it is a loosely reticular labyrinth, whereas in the later-named the cross-connections between the main strands become less and less conspicuous, until in the Pongidae and man it is villous that is to say, composed of rootlets which branch without reuniting by means of side-sprouts. Although there are

s. See Bibliography p. 177

plenty of animals in other orders with discoidal placentas, and many in which the intimate structure of the placenta is of the hemochorial type (Fig. 12), the combination of these features with a completely villous pattern is seen only in the gorilla, orang utan, and man (the chimpanzee's placenta has never received thorough microscopic study). To repeat a statement made in Chapter I, an expert in this field, with slides of all the known placentas before him, would be able to separate those of *Tarsius* and the pithecid primates (monkey-ape-man) from those of all other animals without difficulty, and could then go on with ease and confidence to identify those of the great apes and man because of their striking interresemblance. He might hesitate however before committing himself to a decision as to which came from the gorilla and which from the human species. With respect to the structure of the mature placenta, man is thus definitely closer to the great apes than to any other animals.

But, as we have seen in Chapter I, the organization of the placenta is an outcome of events which take place in early embryonic life. Even in the first two weeks there are great differences in the detailed method of attachment of the embryo to the mother and in the detailed arrangement of the embryonic membranes. In most mammals the embryo implants itself on the surface of the uterine lining in a few it burrows into the maternal tissues. The trophoblast may or may not become thick and invasive. There are differences in the development of the amniotic cavity, whether by folding of the trophoblast or by splitting (cavitation). The extraembryonic mesoblast may appear early or late relative to the differentiation of the embryo itself. The yolk sac may or may not take part in the early stages of placentation the allantois may be large and functional, or medium-sized, or insignificant. In short, the detailed variations of these

* See Chapter I page 81 footnote.

early stages of development are so pronounced that the total picture of implantation and the arrangement of the membranes, in any one kind of animal, becomes an important item in the list of characteristics available for taxonomy and evolutionary comparison.

The reader may review all these facts in §§4 and 5 of Chapter I and the accompanying illustrations. As already stated there, the relevant information is fairly well in hand as regards the human embryo. Fortunately the early stages of the rhesus monkey also are quite fully known, thanks to the intensive work of Streeter, Hartman, and Heuser of the Department of Embryology of the Carnegie Institution, in Baltimore, who have made the development of this monkey better known than that of almost any other mammal. The human embryo and that of the monkey are much alike during the second week, in those details which are significant for comparative study. Both show precocious development of the trophoblast (considerably more pronounced in the human), formation of the amnion by splitting, and early development of the extraembryonic mesoblast. They differ significantly, however, in the type of primary implantation, which is superficial in the monkey, interstitial in the human. With this understanding of the earliest stages of the human species and one of the most typical of the Old World monkeys, we are prepared to turn to the great apes for a comparison which should tell us much.

Alas, the total material for the study of the early development of the great apes consists of two embryos of the chimpanzee, 10½ and 12 days old respectively, at the Carnegie embryological laboratory. The older of the two is very abnormal and thus almost everything that can be said on this great subject depends upon one embryo. The two specimens were obtained in 1938–39 by co-operation of the Yale (now Yerkes) Laboratories of Primate Biology at Orange Park,

Florida. Operations by Carl G. Hartman were done on dates worked out from the menstrual cycles on the basis of previous studies on the reproduction of the chimpanzee by R. M. Yerkes and J. H. Elder and the specimens were prepared and intensively studied by Chester H. Heuser (1940). Their importance with respect to the relation between chimpanzee and man was first pointed out by Dr. Hartman in 1939.

The findings in the case of the 10½-day specimen ("Yerkes A," Carnegie Collection C 620) can be stated in a few words. The embryo is practically identical with human embryos of similar age in every significant detail. The implantation is interstitial and is characterized by very early thickening of the trophoblast. There are certain differences from the human in slight details which may reflect the difference in species, but it is doubtful whether even a trained embryologist, seeing it for the first time, could detect the fact that it is not human.

In short, at the end of 10 or 11 days the human species and one of the great apes (the only one known at that age), are anatomically alike and are different in significant details from the rhesus monkey of a comparable stage and development, although in most respects the embryos of the three species are very similar and must be placed together in a group differing from embryonic mammals of other orders.

It may be added that enough is known about the embryos of the gibbon and siamang (*Hylobates*, *Sympthalangus*) beginning at a stage many days later than the Yerkes chimpanzee embryo, to make it certain that in these apes the implantation is interstitial, like that of man. The same deduction can be made from the late placentas of the gorilla and orang-utan.

Before attempting to evaluate these remarkable facts, it will be worth while to examine very briefly what is known

of the early embryology of other primates. As the reader will realize, there are exceptional difficulties in the way of collecting monkey and ape embryos. To get together a useful series of successive stages of any species by collection in the field requires either special expeditions or the coöperation of scientifically minded residents of the tropics. Pregnant animals, shot or trapped in the jungle, are of course not subject to accurate determination of the stage of pregnancy. To breed monkeys in captivity expressly to get the embryos is an expensive business. Only a few species are hardy in captivity. We know almost nothing about the breeding habits of most of the monkeys. Thus far, only the Carnegie series of rhesus embryos and the two Yerkes chimpanzee embryos have been obtained in that way. Considering these difficulties it is remarkable how much has been discovered by an international group of men, little known to the general public, who have devoted themselves, in the field and in the laboratory, to this bold and far-reaching quest. Emil Selenka (1842-1902) of Erlangen, Germany, opened the modern phase of the subject by his studies of material obtained largely by personal travel in South America and Asia. A. A. W. Hubrecht (1853-1915) made extensive use of his personal connections in the Dutch East Indies, and of his private means, to build up a magnificent collection of primate and insectivore embryos preserved, since his death, in a special institute in his late residence at Utrecht, Holland. Hans Bluntschli of Bern, Switzerland, made valuable collections of New World monkeys during travels in Amazonia. I have already had occasion to mention James Peter Hill, now of London, who made himself a master of marsupial embryology during a long career in Australia and since has contributed greatly to knowledge of the primates. George B. Wislocki, who has advanced our understanding of placentation by studies made at Johns Hopkins and later at Harvard Medical School, Boston, based in

part on his own collections in Central America and George L. Streeter, Carl G. Hartman, and Chester H. Heuser, whose magnificently successful investigation of the embryology of the rhesus monkey was carried out in our Carnegie Laboratory in Baltimore from 1923 to 1939.

Summarizing the work of these and other investigators, we must begin by stating that the lemurs differ from all the other primates in their method of attachment of the embryo to the mother. Instead of a localized massive discoidal or bi-discoidal placenta, the attachment is constituted by interlocking of simple chorionic processes like rudimentary villi with corresponding depressions or down foldings of the maternal surface of the uterus. There is no invasion or destruction of maternal tissue and the placenta is thus of the epitheliochorial type. When the young are born the placenta peels off from the maternal surface, leaving the latter intact in technical terms, the placentation is nondeciduate. The whole arrangement is remarkably like that found in such ungulates as the pig and horse (Fig. 18). Enough is known of the early embryology of various lemurs to show that the amnion is formed by folding and that the allantois attains a fair size and takes part in forming the placenta. In these features also the lemurs differ from the other primates. We shall return to this curious fact later.

Tarsius is next to be considered, that eerie wraith of the East Indian forests, who bears in his tiny body such vaguely disquieting signs of relationship to man that the natives of Sumatra and Borneo stand in awe of him as if he were a ghost, and so for different reasons do occidental men of science, to whom he seems no ghost of a dead past but a portent of the rise of man. The first tarsiers ever brought away alive from their native lands were obtained through the efforts of John F. Fulton of Yale University, who has written an interesting account of his trip to the Philippine Islands in 1938. A. A. W. Hubrecht, who worked out the embry-

ology of *Tarsius*, never saw a living specimen, although he collected more than 450 embryos through contacts he made in the Dutch islands. From his work we know that the embryological development of this primitive primate shows several features that are also characteristic of the higher primates. The blastocyst, for example, very early acquires a direct attachment to the uterine lining. The trophoblast spreads out upon and in the superficial layer of the endometrium somewhat as does that of the rhesus monkey. The placenta is massive, discoidal, and of the deciduate hemochorionic type. The extraembryonic mesoblast develops precociously, giving rise to a body stalk much as in man, and the allantois is never more than a small duct in the body stalk. The yolk sac is small. Unlike the higher primates, however, the amnion forms late by folding of the chorion over the body of the embryo.

In the New World monkeys, which are known only from relatively scanty collections, the amnion forms by splitting the yolk sac apparently develops in some such way as in man and the rhesus monkey, as described in Chapter I, and the extraembryonic mesoblast is formed even more precociously than in *Tarsius*. The allantois is rudimentary. The placenta, which in most species forms in two masses at opposite poles of the chorionic sac, is massive and hemochorionic.

The researches of Streeter and Heuser on the rhesus macaque, typical of the Old World monkeys, have shown that in all these details we are now discussing the monkey resembles man, the only striking difference being that the monkey's blastocyst does not burrow at an early date below the surface of the endometrium, but instead the trophoblast at first invades the surface layer and then spreads out to form the placenta. We have already seen that the great apes, as far as we can be certain from a few placentas of the orang-utan and one of the gorilla and one early embryo of

the chimpanzee, are so similar to man in early development and placentation as to be almost indistinguishable.

Summing up all the available information from the embryo and the placenta, it may fairly be said that if the embryologist were called upon to state his views about the classification of the primates without any knowledge of the anatomy of the adult, he would assemble them in three groups, one containing man and the great apes, one containing the Old World and the New World monkeys, and one containing *Tarsius*.

Whether or not the lemurs form a fourth group of primates, as the comparative anatomists have more or less generally agreed, becomes a very difficult question if embryological evidence alone is considered. Their diffuse epitheliochorial placentation, much like that of pig and horse, is strongly different from that of the ape-monkey-*Tarsius* line. The matter is worth a brief discussion here because in an indirect way it bears on the problem of the position of man. Offhand, we should perhaps naturally assume that the simple, diffuse type of placentation is more primitive, from the evolutionary standpoint, than the massive, complex labyrinthine and villous invasive types. The latter might well be thought to have been evolved from the former. In Chapter I, however, I mentioned G. B. Wislocki's demonstration that the diffuse type of placentation is found in animals of highly specialized kinds, namely the Ungulata, the Cetacea (whales), and the Proboscidea (elephants). Those animals which it is generally agreed are relatively less removed from the general mammalian type, have complex, invasive (deciduate) placentas. Presumably therefore the diffuse nondeciduate epitheliochorial placenta is a secondary departure from the deciduate type. What then shall we think of the lemurs? A recent American writer, H. W. Mossman, goes so far as to suggest that these animals are

not to be classified as primates at all but as close relatives of the ungulates. This radical suggestion disagrees with the findings of comparative anatomists, who consider almost without exception that the adult anatomy of the lemurs indicates primate affinities. The learned J. P. Hill goes to the other extreme from Mossman, reporting details in the early embryology of the lemurs which he thinks indicate an evolutionary transition between them and the deciduate placentas of the higher primates. In short, he believes the ancestors of the monkeys and apes were lemuroid forms. This brings us up against the difficulty that if, as is widely held, the primates evolved from an early ancestor of insectivore type, the lemurs with their diffuse placentation must have been interposed between ancestors and descendants with deciduate placentas! A more commonly accepted conjecture at present is that the lemurs are only collateral relatives of the pithecid (ape-monkey) line and that the type of embryonic membrane formation and placentation found in the lemurs represents a secondary deviation from a stem which had the deciduate placentation.

Evolution, or devolution if you like, from the complex to the simple type of placenta could have taken place in a relatively simple manner. Referring to Fig. 5, B, which represents a blastocyst that has just made contact with the uterus, it will be seen that a genetic mutation at this stage could direct the trophoblast to spread out and to make diffuse contact rather than to invade the uterine wall and form a massive deciduate placenta. Such a mutation, or series of mutations, might well have occurred early in the history of the primate stem, setting the lemurs apart from their kin.

The lesson in all this is that it is not safe to choose any one characteristic, or any limited group of features, upon which to base a theory of relationship among animals. Fundamental and important as the type of implantation and

placentation admittedly is, it cannot outweigh all the other evidences from bones and muscles, brains, teeth, and whatever else the comparative anatomists may be able to cite. The findings of the embryologist must be used in combination with all other available facts. In the case of the lemurs the embryological details alone, as interpreted by some workers, would remove these animals from the relationship with the primates which has been affirmed by the other branches of comparative biology. In the case of man it seems to me the opposite is true—the embryology of our species, as far as we can compare it with our scanty knowledge of other primates, associates man even more intimately with the great apes than does the evidence from comparative anatomy of the adult body. The embryologists, left to themselves, could hardly fail at present to support the most orthodox Darwinian Huxleyan doctrine of the descent of man from an ape-like ancestor, in close relation with the gorilla and the chimpanzee. Knowing, however, the limitations of an approach through any one branch of science in summing up the evidence in the case, all they will insist upon is that the human embryo is that of a primate closely similar to the apes and monkeys. As far as we embryologists are concerned, the comparative anatomists, when they refine their diagrams, may choose to split off the human line either close to the point where the monkeys separated themselves, or close to the stem of the great apes. When we can get early embryos of the gorilla, the orangutan and the gibbons, and more stages of the chimpanzee, we may be able to add something more precise.

If there were space it would be interesting to discuss the broader question of the whole mammalian phylogeny as seen by the embryologists but I shall have to content myself by quoting a recent summing up which may be helpful. The Basel zoologist Adolf Portmann published in 1939 in the international journal *Biomorphosis* (afterward inter-

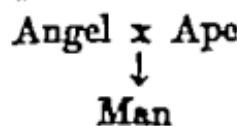
rupted by the war) a classification of the embryonic characteristics of the mammals which I simplify as follows

- 1 Archaic forms (chiefly Insectivora) with massive placenta, comparatively large yolk sac, moderate to large allantois.
2. Evolved groups with small or absent allantois and massive placenta (Chiroptera, Edentata, Rodentia, and Primates)
- 3 Evolved groups with large allantois and diffuse or intermediate placenta (Carnivora, Cetacea, Ungulata)

Reference to Fig. 15 will show that Portmann's scheme fits very well the relationships assumed by Gregory on the basis of comparative anatomy. It differs chiefly in splitting off the rodents from the primitive stem later than the insectivores, but many comparative anatomists at the present day would agree in considering the insectivores the most primitive of living mammals and in supposing that the earliest placental mammals must have been animals of that general sort. Since both comparative anatomy of the adult and embryology agree in seeing many resemblances between the insectivores and the line of Tarsius, monkeys, apes, and man, it follows that our human body in its development and perhaps in its adult structure may have preserved somewhat more of the general primitive mammalian type than many of those animals we are pleased to consider our inferiors. Let us pursue this thought in the concluding part of our study of the natural history of the human embryo.

6

I return to my caller of years ago who thought he could explain man by the simple relation



The collective thinking of mankind, forever struggling to understand this enormously detailed universe in which we find ourselves, inevitably takes comfort in diagrams. Faced with any unsorted array of facts or things, we begin automatically to sort and arrange them, and when they are too large or too subtle to be dealt with directly, we itemize their names on paper, draw lines between them, subordinate one to another, nominate their hierarchies, and rest temporarily content, having achieved in some degree a better ordering of our restless thoughts. Oftentimes, however, the diagram serves too well; it ceases to be the symbol of an explanation and is mistaken for a fact. My friend with the angel-ape theory, indeed, had reached such a stage in his thinking. Thus the progress of science frequently requires not only observation and new classification but the correction of an older synthesis. Sometimes two contradictory diagrams dispute the field, because the new one does not completely replace the old, or because there are two (or more) plausible ways of arranging the facts, or because the true relations have not yet been worked out. The most famous instance of this sort in our own time is the still unresolved conflict of the corpuscular and the undulatory theory of light, in which there are two diagrams each of which fits part of the facts whereas neither one fits all of them.

Something of the same sort exists with respect to the grand question of the nature of man. There are two conflicting diagrams, which may be called the Diagram of the Ladder and the Diagram of the Fan. I have already, in the first chapter, referred to the Diagram of the Ladder, or the Scale of Nature. It is as old as Aristotle, and still in some measure pervades our thought. It simplifies the complexity of nature by arranging all material things in one series of ascending value, from the primeval rock to man. To quote once more Sir Thomas Browne, the great doctor who knew so well how to state with due solemnity the common gropings of religion and science, "There is in this Universe a

Stair, or manifest Scale of creatures, rising not disorderly, or in confusion, but with a comely method and proportion. Between creatures of mere existence, and things of life, there is a large disproportion of Nature, between plants, and animals or creatures of sense, a wider difference, between them and Man, a far greater and if the proportion hold on, between Man and Angels there should be yet a greater." Thus man who was made in the image of God is the head of the hierarchy of earth, by far the uppermost figure in a throng that rises a little way toward the stars.

It is instructive, and something of a warning with respect to our present discussion, to note that Sir Thomas Browne went on to cite the embryology of his day in support of the Diagram of the Ladder "For first we are a rude mass, and in rank of creatures which only are, and have a dull kind of being, not yet privileged with life, or preferred to sense or reason, next in line the life of Plants, the life of Animals, the life of Men, and at last the life of Spirits, running on in one mysterious nature those five kinds of existences, which comprehend the creatures not only of the World, but of the Universe."

This concept of man's nature has of course been closely interwoven with the older thought of Christianity and other dualistic religions. The Diagram of the Fan on the other hand expresses the findings of evolutionary biology. My designation might sound more familiar if I called it the diagram of the family tree, but the trend of all the sciences that have facts to contribute about the evolution of organic life, namely paleontology, comparative anatomy, ecology, and genetics, is toward a scheme that shows any given present-day group of plants and animals as having originated by the relatively sudden output of different evolving forms, rather than by successive divagations like the serial branching of a tree. As someone has remarked, the pattern of evolution within each group is more like a bundle of sticks

radiating from one point than the branching of a tree. To get this idea clearly, take the pictorial diagram of the evolution of the primates (Fig. 16) and split the branches more deeply from the trunk, until the tree almost resembles the ribs of a fan. The point from which the fan spreads out will be the end of one rib of the next earlier stage. To suggest one more analogy, this concept might have been called the Diagram of the Skyrocket, for the whole course of evolution may be likened to one of those multiple rockets that rise in one long flight and then burst again and again, setting off at each burst still other radiating clusters of lights. Thus all the primate lines presumably radiated from some primitive shrew like insectivore and this in turn represented one line among a group that originated from an earlier protomammalian ancestor. That creature was a member of the still earlier radiation that gave rise to the birds, reptiles, and mammals, and so back ultimately to the simplest organisms. But I refrain from insisting upon the analogy of the skyrocket, for it unhappily suggests the presence of a cosmic audience watching the fireworks now being exhibited on this planet, and waiting to see whether the coruscating spark that is mankind is going to burn itself out in the darkness or burst into a family of evolving neo-Hominidae of incalculable sort. Or will it merely die down and drift interminably on, a smoldering relic of the past, like Tarsius or like Limulus the king crab, while the skyrocket of evolving nature gives off new radiations of life from less meteoric sparks?

But let us get back to earth and to safer figures of speech. The two diagrams of the ladder and of the fan, are concerned with two very different estimates of the human body in its relation to man's faith and duty. If all nature is ascending toward heaven through higher and higher corporeal forms, then even the body of man, the noblest creature of earth, is something to be left behind as quickly as pos-

sible, it is an impediment, a burden to the soul that would climb higher still. If it threatens to drag the climber down, let it be neglected and if need be, mortified. The soul will rise higher without it.

To those, on the other hand, who see the human body as that of an animal with a physical history like that of other animals, though endowed with mental qualities of a peculiar kind, no philosophy of life is sound unless it accepts man's animal nature and teaches not humiliation but respect of the body and coöperation of body and mind toward effective activity in this life.

The two concepts both arise naturally from man's daily experiences as a vertebrate with a mind, living in a mysterious universe. Everyone but the unmitigated fanatic and the cynic acts from time to time as if first one, then the other, is true in his own particular case. Each, no doubt, contains something of the truth. Which one gets a hearing in these Terry Lectures in any given year will depend upon the occupant of the rostrum.

7

Under the ancient influence of the Diagram of the Ladder, it is often tacitly assumed that the human body must be in all respects superior to the bodies of other animals. Even professional students of anatomy sometimes share this notion. The young physician who has been given the opportunity to dissect a frog while in high school, a rabbit or cat in college, and a human cadaver in medical school, not unnaturally takes it for granted, as he probes the tissues of his subjects, that he is proceeding consistently from a lower to a higher level of organization. To clarify this point it is necessary to put aside the idea of superiority versus inferiority. We must consider instead the Diagram of the Fan, which symbolizes the fact that animals differ in the degree to which they depart from the general type of their ances-

try Some of the members of an evolutionary radiation acquire highly specialized traits, so that their names must be written upon the right and the left divergent rays of the diagram others continue on the whole to follow the middle path, retaining the pattern of their ancestral line and departing only in few or in minor details. Considered in this way, the human body is surprisingly generalized that is to say, man is in most anatomical features a typical and peculiar vertebrate. As the Vertebrata radiated into their various classes, the Class of Mammalia into its orders, and the Order of Primates into families, genera, and species, the ancestors of the Hominidae were among those which (relatively speaking) held to the middle way, not developing extensive specialization. This is crudely apparent when one considers that there is scarcely any purely physical activity in which man is not excelled by some other animal—neither running, swimming, diving, flying, climbing, nor in withstanding heat and cold, nor in the use of any of the five senses He can, it is true, stand and walk on his hind legs more steadily than any other There is no space here to work out the full technical argument for the generality of the human body Those who wish details will find the whole subject reviewed in *Man's Place among the Mammals* by F. Wood Jones (1929) and in the articles of Adolph H. Schultz and William L. Straus, Jr., listed in the bibliography at the end of this book. In the first place the whole Order of Primates is so highly generalized that zoologists have found it impossible to define a primate by citing characteristics which are peculiar to the order Elephants, whales, rodents, for example, exhibit large and obvious differences from other mammals the primates are characterized only by possessing an aggregate of common characters each of which also occurs in other orders. This fact is illustrated by Mivart's definition of 1873, long used by systematic zoologists, which I will cite in simplified terminology That dis-

tinguished man of science said that a primate is a placental mammal which has finger- and toe-nails and a collarbone its eye sockets are completely surrounded by bone it has three kinds of teeth (incisors, canines, and molars), its brain has a posterior lobe and a calcareous fissure, its thumb or big toe, or both, can be opposed to the other digits, the big toe has a flat nail or none, the animal has a caecum the male has a pendulous penis, and its testes lie in a pouch (scrotum) the female has two pectoral mammary glands. Wood Jones in a forceful passage points out that practically all of these characteristics occur in a large number of non primate mammals, and that most of them are typical mammalian possessions which have been lost in whole or in part by various specialized groups. "The Primate Order is one without distinction, but with essentially generalized mammalian features" It would be going much too far to say that man, a member of this order without distinction, is himself without structural distinction, but it is generally agreed by comparative anatomists that he is not a creature of outstandingly special traits.

Some measure of the generality of man may be drawn up by the method initiated by Tyson, the first dissector of the chimpanzee, by Mivart, and more recently by Sir Arthur Keith and by Schultz, each of whom has chosen a series of anatomical points, listed their occurrence or degree of development in various primates, and compared the list to see how far the anatomy of any one species, thus tabulated, resembles each of the others. The outcome of such a method is to show that man (so to speak) scatters his anatomical likenesses rather widely among the other primates in other words, he has a large array of general features. Since it is impossible for lack of space to illustrate this very large topic with comprehensive references to anatomical facts, I shall quote only one example. The reader may see for himself what is meant by this assertion of the generality of man

if he will inspect in a museum the skeleton of a man's arm and compare it with the fore limb of one of the generalized amphibians, for example *Necturus*, and then with the fore limbs of some of the much nearer but highly specialized relatives such as the dog, the ox, the bat, the whale, and the mole. It will be clear that the primate arm and hand have evolved along the middle way, continuing to resemble the standard pattern, whereas the other animals cited have acquired greatly specialized differences that adapt them respectively to running, to meadow life, flying, swimming, and digging.

Schultz has declared that the human body is a combination of many primitive characters with some that are highly specialized. The most striking specializations are concerned with the size of the brain, which is larger in proportion to body weight than in any other animal of the same size, and with the upright posture, which involves special modifications of the spinal column, the pelvis, and the foot. As to the latter, the studies of W. L. Straus, Jr., on the muscles, and of Schultz on the bones, indicate that the human foot is much more like the general primate plan than might at first be supposed.

It is the brain, then, to which we must look if we would find an organic basis for the self rated superiority of man, but even this organ is built upon the common plan of the vertebrate brain, and as far as gross anatomy goes is so closely similar to that of the great apes that the differences cannot be qualitatively defined. Sir Grafton Elliot Smith's remark has often been quoted, that "No structure found in the brain of an ape is lacking in the human brain and on the other hand, the human brain reveals no formation of any sort that is not present in the brain of the gorilla or chimpanzee." The large size of the human brain, however, and the altered quantitative relation by which the cerebral hemispheres are relatively larger in proportion to the rest

of the brain than in other primates, comprise of course a kind of specialization as significant as if the brain had developed some new lobe unknown in the rest of the animal kingdom. We cannot escape the thought that the anatomical basis of the difference in mental power between man and the apes consists only in the presence of a larger number of cells in the various portions of the cerebral cortex of man and therefore in the possibility of a more intricate cross crossing and registration of nerve impulses.

We can picture the activity of the brain as like that of a general staff headquarters, with its intelligence service, its record rooms, executive command, and communication system connecting all parts of the army. Two armies may be alike in possessing typical equipment, but the one with the larger, better informed staff and the more extensive, more highly integrated communications will have the advantage. Thus the relatively unspecialized human body is guided by a brain which is functionally superior to that of other animals. The creature that owns this combination cannot run or swim as well as many of his fellow creatures, nor can he fly at all without mechanical assistance but his specialized brain can guide his generalized and therefore generally adaptable body to build fast moving cars and ships, and to fly, with a machine, longer and higher than any bird. Were I a preacher or pedagogue, I might go on to pronounce an earnest homily upon the advantages, in the moral as well as the material world, of extreme physical adaptability with extreme cerebral control.

After so long a preamble I come at last to recapitulate what the embryologist has to say about this question of the generalization versus the specialization of man. In the past, human development has been regarded as a very special affair. The rarity and preciousness of early human embryos

seem to confer distinction upon them. Students and investigators necessarily place them in contrast with more plentiful kinds of embryos of the animals of the laboratory and the barnyard. They sometimes forget that classroom embryology is taught and illustrated largely from the birds, which are among the most specialized of all the vertebrates, and from the rabbit and domestic pig, representing two of the more specialized orders of the Mammalia. The rabbit's folded amnion, the pig's immense allantois were familiar long before the quite different nature of those structures in man and the other primates was understood. It is no wonder that the human embryo has seemed peculiar and extraordinary. But as knowledge of a wide range of animals has been obtained early human development has come to be more and more understandable in terms of the general mammalian plan.

The items which have to be considered in discussing the differences between early primate embryos and those of other mammals are (1) the structure of the placenta, (2) the precocious appearance of the extraembryonic mesoblast and the closely related elimination of both the yolk sac and allantois from the function of supplying blood vessels to the chorion, and (3) formation of the amnion by splitting rather than by folding of the chorion.

1 The mere existence of a placental attachment of the embryo to the mother is of course a specialization, one which is sufficient to set apart the placental mammals from the other animals but as already sufficiently shown above in Chapter I, §10 and Chapter III, §5, the type of placenta which characterizes the primates including man no longer seems necessarily to be the end stage of an evolutionary progression from the diffuse epitheliochorial to the massive hemochorial placenta. The analyses of Hubrecht, Wislocki, and Mossman have opened our eyes to the proba-

at by the study of comparative anatomy and of fetal structure.

8

In the foregoing pages of this chapter I have outlined the evidence for two very weighty conclusions about the physical nature of man. The first of these is that he is an animal, a member of the Class of Mammalia, Order of Primates, and closely related to the apes and monkeys. The second is that the human body is not notably endowed with specialized anatomical features of a kind that would fit us to perform limited activities supremely well, but on the contrary is built rather closely to the general mammalian pattern, and therefore can perform varied tasks under the guidance of a superior brain. As the reader must have noticed, what I have said about the contribution of embryology to this subject, which after all is the real theme of the discourse, has largely consisted in the removal of embryological objections to these two conclusions. The difficulties which delayed the investigation of early human development, together with a certain prideful if often unconscious expectation that human structure must always exhibit superiority to other animals, even in its earliest gestation, have given a false impression that the human embryo is exceptional. Against this idea I have shown that recent investigations, involving a great increase in our knowledge of the early embryonic stages and of placentation, have not only strengthened our sense of the affinity of man to other animals but also tend more and more to agree with the declarations of comparative anatomy as to the generality of his bodily structure.

Let us pause a moment to reflect that generalized organisms possess a degree of liberty in action which is denied to more specialized creatures. In Chapter II we saw that the evidence from embryology points to a kind of foreordination

tion, not exactly that of the theologians but none the less operative to determine the fate of countless human beings. In this present chapter we are led, on the other hand, by the evidence from comparative anatomy to ponder upon the freedom of the will, or at least freedom of action, which we have because our bodies are versatile, untrammelled by specialization for extreme but particular skill, and capable of any task the mind may imagine. The way of an eagle is to fly, the way of a fish is to swim, but a man's way is to kill or to cultivate, to grovel or stand erect, to dissipate or to build. Because he has a generalized body he can eat any diet, live in jungle, prairie, or upland, swim across rivers or scale mountains, build altars to many gods. If anyone insists that all this freedom inheres in the mind alone, let him name a valiant deed or a crime that does not depend also upon the anatomical versatility of our bodies, or cite any great life that could have been lived by a man with bat's wings or the alimentary canal of a sheep. The scope of the human mind, the freedom of human decision, are bound up inextricably with the generalization of the body.

The animal nature of man is an old story, as old or older than the Scripture with which I have adorned the title of this chapter but it must be retold in each age and restudied in the light of all that science can learn, for the whole structure of our laws, our philosophy, and our religion depends upon the way in which we look at human nature. We shall always have among us, of course, those who decry the body and deprecate its claims in the interest of the soul among them, be it said many noble persons, gaunt saints and shining heroes who have taught their fellow men how to glorify the flesh by following the spirit. And yet such deeds as theirs, and every act of love and sacrifice, even man's dreams of beauty and his prayers to heaven, must be realized with the flesh, bones, and organs of an animal that is blood brother to the worm and the ape.

Who should know this better than the physician-scientist whose privilege it is to observe the frail minuscule germ of our race in its earliest days, and who sees constantly in his work what I have tried to tell in these chapters that we begin our lives in continuance of a long past and in progression toward an unseen goal that life is precarious from the first day to the last, under the sway of events we can neither comprehend nor calculate and that we bear through all our days the marks of intimate kinship with the animal world, tempered by powers of the mind that bestow dignity and honor upon the life of the body

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